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REVIEW

Barriers in Healthcare to the Use of Optical Coherence Tomography Angiography in Multiple Sclerosis

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ABSTRACT

Optical coherence tomography angiography (OCT-A) is a state-of-the-art imaging technique for the retinal vasculature to accurately segment the capillary network and assign it to retinal layers. OCT-A is a promising technique to better understand neurological diseases with visual system manifestations, such as multiple sclerosis (MS), and to identify and characterize vascular biomarkers. Initial studies suggested vascular changes in MS and its differential diagnoses such as myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and neuromyelitis optica spectrum disorder (NMOSD). Here we review clinical and technical aspects of OCT-A imaging and discuss the potential for the MS field as well as barriers that need to be overcome before OCT-A can be established in clinical application.

Keywords: Barriers in healthcare; Clinical application; Multiple sclerosis; Optical coherence tomography angiography

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Key Summary Points

Vascular changes are of increasing interest in multiple sclerosis (MS) and its differential diagnoses.

The retinal microvasculature might be a promising marker for early diagnosis and sensitive monitoring in MS and its differential diagnoses.

Optical coherence tomography angiography (OCT-A) has the potential to serve as a non-invasive multivariable quantification tool for the retinal vascular system, and this might replace more expensive, invasive and/or complex techniques.

In MS, the retinal vascularity shows a reduction in parafoveal and peripapillary vessel density (VD) on OCT-A, with a higher decrease in optic neuritis (ON) eyes, and is associated with the disease duration and the disability.

Barriers such as the lack of guidelines and standardized postprocessing methods have to be overcome before OCT-A can be integrated into clinical practice.

BACKGROUND

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS). It is characterized by inflammatory demyelination leading to axonal degeneration. MS affected 2.8 million people worldwide in 2020 and has an especially high prevalence among young people [1]. Women are more frequently affected than men, with a ratio of around 2 to 1 [1]. MS has been subdivided into the distinct subtypes of relapsing–remitting (RRMS), secondary progressive (SPMS) and primary progressive MS (PPMS) as well as clinically isolated syndrome (CIS). Yet, recent research challenges this subdivision and suggests overlapping disease processes [2–4]: In particular, progression independent of relapse activity (PIRA) is of increasing interest, but its pathological process is not well understood [5]. PIRA may occur in any stage of the disease and is associated with unfavorable long-term outcomes, especially if it occurs early in the disease course [6].

In most people with MS, the visual system is affected: Optic neuritis (ON) is one of the most common onset symptoms and is experienced by most people with MS at least once during the disease course, leading to acute edema and retinal inflammation and subsequently to severe neurodegeneration of retinal ganglion cells and their axons in the retina and optic nerve. Patients experience pain with eye movement, vision loss and red desaturation, but they often recover well. As it is part of the CNS, the retina also undergoes attack-independent neurodegeneration in MS beyond healthy aging [7]. In clinical management, it is important to recognize the visual function, given that patients rank this as one of their crucial bodily functions [8], and there is evidence indicating that a loss of visual function is associated with a reduction in quality of life (QoL) [9, 10].

It is essential that differential diagnoses such as neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are considered in the diagnostic workup of MS, as they may present similar symptoms and clinical findings but differ in therapy and prognosis. NMOSD is often associated with aquaporin-4 antibodies (AQP4-IgG) and diagnosed in accordance with the criteria [11] as well as MRI and clinical findings [12]. People with MOGAD have myelin oligodendrocyte glycoprotein antibodies (MOG-IgG) and show some distinguishing clinical and MRI features [13, 14]. Similar to MS, ON is a common clinical symptom in NMOSD and MOGAD. Yet, patients with NMOSD and MOGAD often have bilateral and more severe ON leading to drastic retinal neurodegeneration [15]. Clinical and neuro-ophthalmological findings on the distinction between MS, NMOSD and MOGAD are extensively reviewed elsewhere [16, 17]. In addition to NMOSD and MOGAD, rheumatic diseases such as Susac syndrome (SS) and sarcoidosis, mitochondrial optic neuropathies such as Leber's hereditary optic neuropathy (LHON), vascular diseases such as non-arteritic anterior ischemic optic neuropathy (NAION),

and infectious diseases such as syphilis must also be considered in the diagnostic workup [18, 19].

The ON-dependent and ON-independent retinal neurodegeneration in MS can be quantified by optical coherence tomography (OCT), a non-invasive high-resolution imaging method [20]. Primarily, a thinning of the retinal nerve fiber layer (RNFL) and the combined ganglion cell and inner plexiform layer (GCIPL) has been used as a marker of retinal neurodegeneration after ON [7]. Additionally, inflammatory changes can be detected and monitored reliably, sensitively, and objectively with OCT [21].

Recently, vascular changes in MS and its differential diagnoses have become of increasing interest because 1) hypoxia is presumed to play a key role in the pathogenesis of neuroinflammation, and the microvasculature might thus be a promising marker to describe subclinical progress and recognize early disease activity [22, 23]; 2) MS patients have a higher risk of ischemic stroke, which might be caused by endothelial dysfunction and predisposed by cerebral hypoperfusion [24]; and 3) due to the distinct pathologies in MS and its differential diagnoses, specific vascular changes might contribute to the diagnostic workup or monitoring of PIRA [25].

To better understand the role of the vasculature in MS, the microvasculature of the ocular fundus can be imaged by OCT angiography (OCT-A). This is a relatively novel technology based on OCT, which generates high-resolution three-dimensional images of the retinal capillary network. This article reviews the current literature on and potential applications of retinal vasculature changes in MS and its differential diagnoses as well as current barriers to the application of these imaging methods in clinical practice.

RETINAL VASCULATURE ANATOMY

The retina is one of the most metabolically active structures in the human body. Its vasculature consists of larger arteries and veins (macrovasculature) and a capillary network (microvasculature). The central retinal artery (CRA) supplies the inner retinal layers and has an approximate diameter of 135 µm, as compared to the central retinal vein (CRV), which has an approximate diameter of 151 µm [26].

The CRA and CRV branch out at the posterior pole into a capillary network that can be identified in the nerve fiber layer (NFL), ganglion cell layer (GCL) and inner plexiform layer (IPL). The deepest capillary network is found at the boundary of the deep inner nuclear layer (INL) and outer plexiform layer (OPL). The capillary network consists of vessels with a diameter of approximately 8 µm, and its greatest density occurs in the GCL [27]. Vessels are absent in the central region of the macula, which is called the foveal avascular zone (FAZ).

TECHNICAL PRINCIPLE OF OCT-A

OCT-A is a non-invasive imaging technique that provides a quick, high-resolution, three-dimensional visualization of perfused vasculature of the retina and choroid. OCT-A is mainly used in the macula and optic disc area, but can also visualize the microvasculature in peripheral regions of the retina when the assembling angiography mode is used [28].

The OCT-A technique is based on OCT, which analyzes the intensity of reflected light. Upon performing repeated scans at each location, OCT-A enables the detection of moving particles such as erythrocytes flowing through vessels. Due to the stability of the surrounding structures, the algorithm can separate static surrounding tissue from the perfused vessels [29]. OCT-A technology is provided by different companies; their products differ mainly in their technical specifications, such as the scan time, scan pattern (3 × 3 mm to 12 × 12 mm), wavelength (840–1050 nm) and resolution (~ 2 to 5 µm axially and 5–20 µm laterally); usually, the resolution is decreased for an increased scan pattern size.

During postprocessing, the capillary network can be segmented by a variety of non-commercial algorithms [30–33], assigned to retinal layers and then presented in a two-dimensional binary image (Fig. 1).

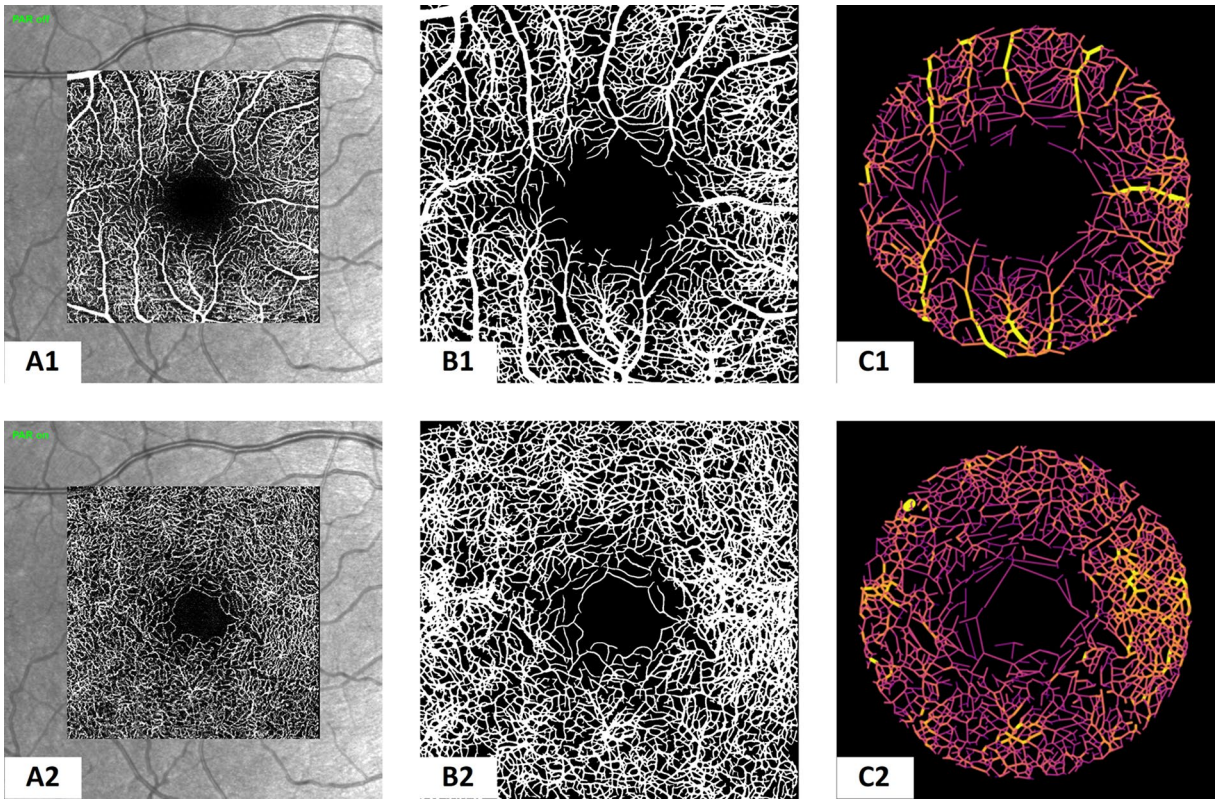

Fig. 1 Optical coherence tomography angiography (OCT-A) scan (pattern size: 3 × 3 mm) of the superficial vascular complex (**A1**) and deep vascular complex (**A2**) by a Spectralis OCT-A from Heidelberg Engineering (Heidelberg, Germany), detailed vessel segmentation (**B1**/**B2**, 3 × 3 mm) and blood flow visualization (**C1**/**C2**, 2.5 × 2.5 mm) using a non-commercial algorithm of Kreitner et al. (published in 2024) [30]

Quantitative metrics extracted from these images typically include the size of the FAZ and the vessel density (VD). By applying additional methods, extended metrics, including vessel tortuosity and the complexity of the vascular network (fractal dimension), can be used [32].

For quantification, the capillary network is usually divided into three complexes: the superficial vascular plexus (SVP), the deep vascular plexus (DVP) and the radial peripapillary capillary plexus (RPCP). Each plexus is delimited based on the retinal layers, as shown in Fig. 2. Most commonly, the SVP is delimited internally by the inner surface of the internal limiting membrane (ILM) and externally by the IPL. The DVP is delimited internally by the IPL and externally by the OPL. The boundaries are defined and calculated slightly differently and have partly different names depending on the device that is used (e.g. DVP with the Angioplex by Carl Zeiss Meditec versus deep vascular complex (DVC) or deep capillary plexus (DCP) with the Spectralis OCTA by Heidelberg Engineering) (Fig. 2).

The benefits of OCT-A compared to more traditional imaging methods such as fluorescein angiography (FA) and indocyanine green angiography (ICGA) are mainly due to the non-necessity for contrast agents and include the low risk for allergic reactions and the option for frequent repetition due to the non-invasiveness of OCT-A. Further, OCT-A can image all layers of the retinal vasculature, whereas FA has limitations when visualizing the radial peripapillary or deep capillary network [34]. However, OCT-A postprocessing algorithms are still limited by the reduced light penetration in deeper layers and by image artifacts projected from inner to outer layers.

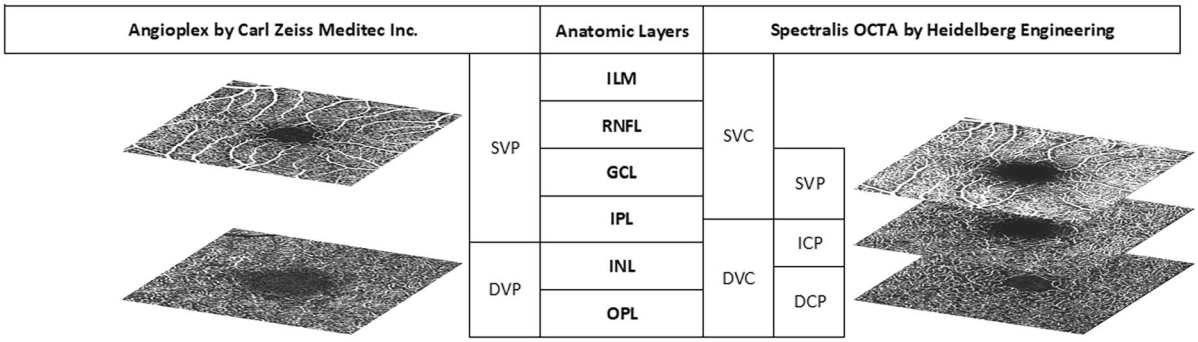

Fig. 2 Visualization of the macular segmentation plexus in optical coherence tomography angiography scans (OCT-A). The anatomic layers listed from the inner to the outer layer are as follows: internal limiting membrane (ILM), retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL). The boundaries considered when the plexus analysis is performed by different OCT-A devices (using the Angioplex from Carl Zeiss Meditec Inc. and the Spectralis OCTA from Heidelberg Engineering (Heidelberg, Germany) as examples) are shown along with the appropriate segmented two-dimensional image of the retinal capillary network for each plexus: *SVP* superficial vascular plexus, *DVP* deep vascular plexus , *ICP* intermediate capillary plexus, *SVC* superficial vascular complex, *DVC* deep vascular complex, *DCP* deep capillary plexus

RETINAL VASCULAR CHANGES IN MS

MS causes not only neuroinflammatory and neurodegenerative changes but also changes in the retinal vascularity: reductions in parafoveal VD in the SVP and in peripapillary VD in MS are described in several studies ([35–37]). In contrast, a reduction in the DVP is rarely seen [35, 38] or not observed at all [39].

With regard to the subtypes of MS, to our knowledge there are currently no published data on OCT-A in people with CIS and PPMS. One study suggested a sectoral significant reduction in VD in RRMS [40]. A comparative analysis of RRMS and SPMS showed a decrease in VD and perfusion density in SPMS compared to RRMS, with the greatest reduction observed in SPMS with ON [41].

The history of ON appears to be an important contributing factor to the development of retinal vascular changes in general. A systematic review, which mainly included data from patients with RRMS but also data from patients with other subtypes of MS as well as NMOSD, showed a significant difference in peripapillary VD and VD of the SVC between the ON group (4.96%/4.30%) and the non-ON group (2.28%/2.27%), with a higher decrease in ON eyes [39]. Further, no vessel loss was observed in the fellow eyes or in eyes of patients experiencing non-ON relapses (RRMS or CIS), but ON eyes showed a reduction in the VD of the SVC that reached a plateau between 90 and 180 days, within a first significant vessel loss occurred early after acute ON [42].

The results suggest that the atrophy of neuronal and axonal structures and the reduced VD are closely pathophysiologically linked. Three potential explanations for this currently exist, all of which might contribute to the effect. Firstly, neurodegeneration might lead to reduced metabolic activity and a lower oxygen demand within the RNFL and GCIPL. This could then lead to reduced local blood perfusion as detected by OCT-A and subsequent to the regression of blood vessels. This would also explain why the SVP is more affected than the DVP, as the SVP supplies the RNFL and GCIPL. Secondly, microvascular abnormalities could be part of the primary pathology inducing neurodegeneration. However, neurodegeneration would then be expected to occur after retinal microvascular change, which has not been observed so far. Thirdly, the neurodegeneration and the rarefication of the microvasculature could both be caused by the inflammatory process.

With regard to vision-related QoL, there are currently no published data on the retinal vasculature. However, there is evidence indicating that reduced VD in the SVP is associated with disease duration, visual acuity (high and low contrast visual acuity) [37] and disability (measured by Expanded Disability Status Scale) in MS [37, 43].

Some studies report conflicting results about retinal vascular changes in MS, including an unaffected flow index (MS with and without ON) [44] or even increased VD (MS without ON) [38, 45] in parafoveal SVP. Yet, differences in cohort characteristics (such as sex, ethnicity, small sample size), and heterogenous pre- and postprocessing methodologies are still a challenge to comparability.

RETINAL VASCULAR CHANGES IN DIFFERENTIAL DIAGNOSES OF MS

People with NMOSD seem to undergo changes in retinal microvasculature that are distinct from MS. Distinctions were first detected upon analyzing fundus photography, and they suggest that the neurodegeneration in NMO might be mediated by vascular changes [25]. Recent studies using OCT-A showed a significant association between parafoveal and peripapillary VD with neurodegenerative OCT parameters in both MS and NMOSD [46]. People with NMOSD showed decreased VD of the SVP (termed the superficial retinal capillary plexus in that work) compared to people with MS [46, 47]. In both people with MS and people with NMOSD, the peripapillary VD is significantly lower in ON eyes than in non-ON eyes, with a greater reduction in NMOSD-ON than in MS-ON eyes [48]. This could be due to more severe neurodegeneration in NMOSD or due to a potential astrocytic disease component in connection with the antibody against AQP4, an astrocytic water channel [49]. Astrocytes are presumed to play a crucial role in modulating cerebral blood flow in response to neuronal activity, ensuring an adequate supply of glucose, oxygen, fatty acids and amino acids to neurons [50, 51]. Thus, OCT-A could be a promising method for the quantification of vascular changes caused by astrocytic disease, as suggested by AQP4-IgG seropositive NMOSD.

Little is known about retinal vasculature changes in people with MOGAD. One study suggests a decrease in VD in the peripapillary and parafoveal areas, with a greater decrease as the number of ON episodes increases [52].

There is also limited information about OCT-A use in other differential diagnoses such as SS, sarcoidosis and LHON; however, initial findings indicate changes in the retinal vascularity: patients with SS are affected by retinal vascular changes [53], but they are less specific and mainly depend on the affected area, with greater involvement in the DVP [54, 55]. A notable alteration in the DVP is also observed in ophthalmologic manifestations of sarcoidosis, whereby the VD in the SVP also appears reduced [56]. Findings on Sjögren's syndrome suggest that ocular microvascular alteration can also be observed in rheumatic diseases [57], such that OCT-A may be a valuable tool for differentiating MS from rheumatic disorders [58]. Finally, parafoveal [59] and peripapillary [59, 60] microvascular changes were detected over the different stages of LHON, with the greatest reduction in VD typically occurring in the chronic stage. So far, the potential application of OCT-A in differential diagnoses is still limited due to the heterogeneous study designs and cohorts.

RETINAL VASCULAR CHANGES IN COMORBIDITIES

With increasing age and worsening health, the comorbidities increase and have a greater impact on imaging findings in MS and differential diagnoses.

A decreased retinal VD has been observed in patients with diabetes mellitus (DM), particularly in the DVC [61]. Even without a clinical retinopathy, microvascular impairments were detected in patients with DM [62]. Subgroup analyses suggest that patients with DM type 1 are less affected than those with DM type 2 [62, 63], that females may have earlier and more microvascular damage than males [64] and

that vascular alterations are associated with the disease duration [63, 65]. Furthermore, alterations in the SVP, DVP and RPCP are described in patients with systemic hypertension (HTN) as well [66, 67], and they appear to be affected by the duration of the HTN [68] and the intensity of the treatment [69]. Additionally, one study suggests that the presence of HTN in patients with DM results in a more severe reduction in the peripapillary microvasculature [70]. Patients with a major depressive disorder (MDD) also show a decreased VD [71]; however, no correlation between the extent of vascular change and the disease severity has been identified [72]. Further, ocular pathologies such as glaucoma [73] and high myopia [74], which may be present in patients with MS, also reduce macular and peripapillary VD.

It is important to acknowledge that a physiological decline in retinal vascular density also occurs with aging itself [75, 76]. If and how the VD changes that occur in MS can be distinguished from comorbidities and aging has not been studied so far. Meanwhile, it is crucial to describe the comorbidities and consider them in analyses.

CURRENT AND FUTURE APPLICATIONS OF OCT-A IN MS

The introduction of OCT-A provides new insights into vascular pathology in MS and its differential diagnoses. Initial study results show changes in the vascular network in MS, MOGAD and NMOSD, with and without ON. A few insights into SS, sarcoidosis, LHON and rheumatic disorders have been reported, and a modest number of studies have also explored the potential of the retinal microvasculature when differentiating MS from differential diagnoses.

In the future, OCT-A may play an important role in the differential diagnosis and in quantifying, monitoring and predicting disease activity, visual outcome and vision-related QoL, but further work will be necessary to better understand its potential. Further, a model of both the retinal neurodegeneration and microvascular changes might provide promising markers for the differential diagnosis in the future.

BARRIERS IN CARE TO THE APPLICATION OF OCT-A IN MS

Several barriers to the implementation of OCT-A in clinical practice for people with MS still exist.

Firstly, guidelines are needed that are supported by quantitative clinical data. Currently, there is no agreement on set standards for segmentation and quantitative metrics that are uniformly defined. An improvement in standardized image postprocessing and interpretation will be necessary to recognize vascular abnormalities and to manage imaging errors and artifacts such as projections caused by the limitations of the technology. Further studies are also required to establish clear guidelines for the differentiation of vascular changes caused by MS from those caused by comorbidities and physiological changes, such as age-related changes [77].

Secondly, the image quality has a strong impact on the interpretability of OCT-A images [78]. Patients need to maintain a high level of concentration and focus during the examination, which is particularly difficult for older and/or disabled people. In regard to MS, the number of artifacts in OCT-A images is correlated with disease duration, disability progression and severity of ON history [79]. Thus, quality control is essential. Based on OSCAR-IB [80, 81], a first and promising approach for the quality assessment of OCT-A was developed by Wicklein et al. [82]. Further validations across different centers, devices, demographics and diagnoses to ensure sufficient image quality and reproducibility data will be necessary before it is implemented in clinical practice.

Artificial intelligence (AI)-based technology has the potential to overcome traditional limitations and accelerate the clinical application of OCT-A. The use of deep-learning-based segmentation methods trained with synthetic data promises a more accurate and robust image analysis and segmentation of blood vessels. Furthermore, AI models have the advantage of

detecting pattern changes in the microvasculature and may thereby uncover novel features that contribute to the identification of retinal biomarkers.

OUTLOOK

Recent research suggests that OCT-A can contribute to our understanding of the mechanisms of neuroinflammatory diseases such as MS. In the future, quantitative metrics of retinal microvasculature changes might be applied in differential diagnoses and when monitoring the disease activity of people with MS.

OCT-A has the potential to serve as a precise, non-invasive, multivariable quantification tool of the vascular system, and it might replace more expensive, invasive and/or complex techniques. However, standardized analytical methods and guidelines, improvements in image quality, and increasing experience in interpretation, especially in neuroinflammatory diseases, are needed before OCT-A can be integrated into daily clinical practice.

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Declarations

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