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REVIEW

Optical Coherence Tomography Angiography in Neurodegenerative Diseases: A Review

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Background: Optical coherence tomography angiography (OCT-A) has emerged as a novel, fast, safe and non-invasive imaging technique of analyzing the retinal and choroidal microvasculature in vivo. OCT-A captures multiple sequential B-scans performed repeatedly over a specific retinal area at high speed, thus enabling the composition of a vascular map with areas of contrast change (high flow zones) and areas of steady contrast (slow or no flow zones). It therefore provides unique insight into the exact retinal or choroidal layer and location at which abnormal blood flow develops. OCTA has evolved into a useful tool for understanding a number of retinal pathologies such as diabetic retinopathy, age-related macular degeneration, central serous chorioretinopathy, vascular occlusions, macular telangiectasia and choroidal neovascular membranes of other causes. OCT-A technology is also increasingly being used in the evaluation of optic disc perfusion and has been suggested as a valuable tool in the early detection of glaucomatous damage and monitoring progression.

Objective: To review the existing literature on the applications of optical coherence tomography angiography in neurodegenerative diseases.

Summary: A meticulous literature was performed until the present day. Google Scholar, PubMed, Mendeley search engines were used for this purpose. We used 123 published manuscripts as our references. OCT-A has been utilized so far to describe abnormalities in multiple sclerosis (MS), Alzheimer's disease, arteritic and non-arteritic optic neuropathy (AION and NAION), Leber's hereditary optic neuropathy (LHON) papilloedema, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), Wolfram syndrome, migraines, lesions of the visual pathway and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). It appears that OCT-A findings correlate quite well with the severity of the aforementioned diseases. However, OCT-A has its own limitations, namely its lack of wide-field view of the peripheral retina and the inaccurate interpretation due to motion artifacts in uncooperative groups of patients (e.g. children). Larger prospective longitudinal studies will need to be conducted in order to eliminate the aforementioned limitations.

Keywords: optical coherence tomography angiography, neurodegenerative diseases, neuro-ophthalmology

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Introduction

Optical Coherence Tomography Angiography (OCT-A) is a recently introduced imaging modality which is used mainly for the assessment of the integrity of the retinal vasculature in a wide range of retinal vascular diseases.[1–5] OCT-A has also been utilized for the assessment of the blood perfusion of the optic nerve head in patients suffering from glaucoma.[6]

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The use of OCT-A in the assessment of the retinal vasculature was approved by the Food and Drug Administration (FDA) approximately 4 years ago. The principles of OCT-A imaging are the same with the conventional OCT.[7]

This newly introduced imaging modality has some advantages compared to the conventional retinal imaging modalities. Firstly, it allows an en-face high resolution and enhanced depth imaging of the retinal vascular network.[8] Unlike fluorescein or indocyanine green angiography, OCT-A is non-invasive. This means that the patients do not have to receive intravenous injections of a dye and this essentially eliminates all the side effects that the conventional retinal angiography techniques have including anaphylaxis, nausea, vomiting, rash, urine and skin discoloration. As a result, OCT-A is also much safer and better tolerated compared to fluorescein or indocyanine green angiography. In addition, the fluorescein and indocyanine green dye injection have been found to create obscurations of the retinal imaging and this may result in poor quality pictures and subsequently inability to address relevant changes in the retinal vascular network, such as capillary loss, early neovascular membrane formation or vessel distortion.[9–13] On the other hand, OCT-A does not require injections of dye and therefore the quality of the images obtained seems to be superior compared to the ones obtained by fluorescein or indocyanine green angiography.

Given all the above significant advantages of OCT-A, its use has been gaining increasing popularity among the Medical Retina Specialists. At the same time, there is a lot of debate as to whether OCT-A could also be used in Neuro-ophthalmology and Neurology.

The retinal vascular network exhibits striking similarities with the vascular network of the brain.[14,15] Due to the limitations faced in terms of accessing the brain vasculature, the vascular network of the eye could potentially serve as a mirror reflecting the changes of the brain vasculature in other neurodegenerative diseases. This has prompted the use of OCT-A in animal models for the study of brain injury and stroke.[16] Furthermore, there have been recent publications where the use of OCT-A was explored in other neurological and neuro-ophthalmological diseases.[17–28]

In this manuscript, our aim is to summarize the basic principles and algorithms of OCT-A. We also aim to summarize the salient findings that have been published so far about its use in the fields of Neuro-ophthalmology and Neurology, which are two scientific fields with significant overlap. Furthermore, we would like to point out the limitations in the use of OCT-A. Finally, we would like to make suggestions on how to expand its application in diseases, where its use has been limited or absent so far.

Materials and Methods

We tried to perform a thorough and extensive review of the current literature up until the present day (May 2020). Google Scholar, PubMed, Mendeley search engines were used for this purpose. The terms "optical coherence tomography" "optical coherence tomography angiography", "Neuro-ophthalmology" and "Neurology" were typed in the aforementioned search engine tools in order to identify publications that are related to the use of OCT-A. Other associated terms were also used including optic neuropathy, visual pathway, neurodegeneration, cognitive impairment, demyelination, diabetic retinopathy, Alzheimer's, papilloedema, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS) and stroke. We used approximately 130 published manuscripts as our references, which were published mainly from 2015 until the present day and were pertinent to the topic and contained descriptions specifically about OCT and OCT-A and their applications in neurological and neuro-ophthalmological conditions. The rationale behind our focus from the year of 2015 onwards was the fact that OCT-A was granted FDA approval that year.

Basic Principles and Algorithms in OCT-A

There are a few algorithms which are utilized by different OCT-A devices currently available in the market to obtain images of the retinal vasculature. These include ultrahigh-sensitive optical microangiography (OMAG, Cirrus HD-OCT 5000™, Carl Zeiss Meditec. Inc),[29] split-spectrum amplitude decorrelation angiography (SSADA, Optovue RTVue XR Avanti™, Optovue Inc., Fremont, CA),[30] OCT Angiography Ratio Analysis (OCTARA, Topcon DRI OCT Triton Swept source OCT™, Topcon, Japan), and full-spectrum amplitude decorrelation algorithm (FS-ADA, Spectralis OCT2 module prototype™, Heidelberg Engineering, Germany)[31] (Table 1). These commercially available devices produce A-scan images that are three-dimensional (3×3 mm2 A lines in cross-sectional images or 1 pixel in the enface image in less than 3 s.). The frequency of the A-scan varies among the commercially available devices mentioned above. The A-scan images then are merged and produce the B-scan images.[7] The commercially available OCT-A devices can produce images with wide field of view, but the lateral resolution of the images is poorer.[7] For wide field of view and simultaneously high-resolution

Table 1 Commercially Available OCT-A Appliances

Manufacturer	Details
ZEISS Angioplex™	OCT angiographic imaging on the CIRRUS™ HD-OCT platform, with a scanning rate up to 68,000 A-scans per second and an improved tracking software known as FastTrac™. A three-dimensional image is obtained depicting erythrocyte flow as well as the microvasculature of the superficial, deep, and avascular layers of the retina.
ZEISS PLEX Elite 9000 Swept-Source OCT Angiography	Uses a line-scanning ophthalmoscope (LSO) with super-luminescent diode laser beam of 750 nm. Allows clinical researchers the potential to see deeper, wider and in more detail from the vitreous to the sclera in the posterior segment.
Optovue AngioVue® (Optovue, Inc., Freemont, CA, USA)	Uses split-spectrum amplitude-decorrelation angiography algorithm, which minimizes motion noise. This system also allows quantitative analysis, since it provides numerical data about flow area and flow density maps.
RTVue XR Avanti (Optovue Inc.)	Enables simultaneous three-dimensional (3D) structural imaging of the retina and generation of en face maps of blood flow through a split-spectrum amplitude decorrelation angiography algorithm. Upgraded Version of Optovue AngioVue®
Topcon® DRI OCT Triton Swept source OCT	Uses a different algorithm, OCTA RatioAnalysis, which benefits from being paired with SD-OCT, and improves detection sensitivity of low blood flow and reduced motion artifacts without compromising axial resolution. SMARTTrackTM is a very useful tool to compensate for the ever-present involuntary eye movements (microsaccades). It allows the automatic acquisition of a follow-up scan in precisely the same anatomical location. SMARTTrack™ enhances the user-friendliness of the machine.
Heidelberg engineering®	Uses the active eye-tracking system (TruTrack™) that assesses simultaneously fundus and OCT images acquisition in order to achieve a better signal-to-noise ratio.

images, swept source OCT-A devices can be utilized[32,33] or wide-field montages.[29]

In order to detect blood flow in the OCT images, the B-scan images are repeated at the same cross-sectional area with similar scanning protocols that are used in other OCT-A devices.[33,34] In fact, blood flow detection is essentially achieved by the detection of motion of the red blood cells. SSADA utilizes de-correlation values between the repeated B-scans.[35] An increase in these values suggests blood flow, whereas areas of reduced values represent areas of non-perfusion.[35] Unlike SSADA, OCTARA utilizes intensity ratio analysis to detect blood flow, whereas FS-ADA utilizes motion contrast.[7,36]

As it was mentioned in the beginning of the manuscript, the principles of OCT-A imaging are the same with the conventional OCT. This allows the acquisition of images of the retinal vascular network of a specific retinal layer through segmentation.[37] The OptovueTM exploits this principle by dividing the retina to five different regions: a) The Inner Retina (from ganglion cell layer to inner plexiform layer) b) The Middle Retina (from inner nuclear layer to outer plexiform layer) c) The outer retina (from outer nuclear layer to external limiting membrane) d) The Choriocapillaris e) The choroid.[1,7] These regions can be assessed for the presence of new vessels, loss of capillary perfusion and increased vessel tortuosity by using qualitative data.[38–40] The OptovueTM software also contains the ability to use quantitative data through fractal analysis or pixel counting methods to assess the fovea avascular zone (FAZ), parafoveal area and areas of foveal non-perfusion but also other peripheral retinal areas as well by using decorrelation values.[30,35]

OCT-A in Healthy Individuals

There have been publications that describe the appearances and flow of the retinal vasculature in otherwise healthy individual volunteers.[41] The findings were very valuable to establish how a normal vasculature should be and, subsequently, this helps identify the abnormalities on OCT-A that are attributed to a pathological entity e.g. vein occlusion. In summary, OCT-A in otherwise normal controls reveals an even blood flow in both the deep and superficial vascular plexuses and clear visualization of the retinal and choroidal layers.[30] These OCT-A findings have been also confirmed in the histological examination of post-mortem specimens.[42]

After having described the basic principles and algorithms of OCT-A, its advantages over the conventional

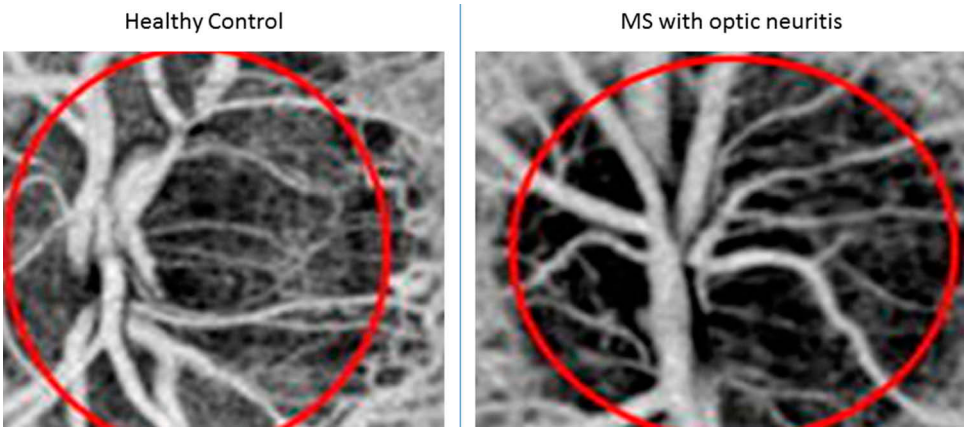

Figure 1 Left Side: Disc OCT-A of a healthy control subject. Right side: Disc OCT-A of an optic neuritis disc showing reduced density of the optic nerve head blood vessel network. This implies reduced blood flow on the optic nerve head.
Notes: Red solid lines indicate the ONH area that was used for the relevant flow index calculations. Copyright © 2014. BMJ Publishing Group Limited. Modified from Wang X, Jia Y, Spain R, et al. Optical coherence tomography angiography of optic nerve head and parafovea in multiple sclerosis. *Br J Ophthalmol*. 2014;98:1368–1373.[17]

angiography retinal imaging techniques and how a normal OCT-A looks, we will try to summarize the abnormal OCT-A findings in different neuro-ophthalmological disorders. After extensive literature search in Google Scholar and PubMed, OCT-A has been utilized so far to describe abnormalities in multiple sclerosis (MS), Alzheimer's disease, arteritic and non-arteritic optic neuropathy (AION and NAION), Leber's hereditary optic neuropathy (LHON), papilloedema and pseudopapilloedema, diabetic retinopathy, Parkinson's disease and its variants, amyotrophic lateral sclerosis (ALS), Huntington's disease and finally in miscellaneous neurological disorders.

MS

MS is a chronic neurodegenerative disorder that is characterized by an inflammatory process that leads to demyelination in different regions of the central nervous system (CNS). Optic neuritis can be the initial symptom in approximately 25% of patients and up to 50% of MS patients will suffer from at least one episode of optic neuritis during the course of their disease.[7,20] In post-mortem histological specimen examination, it has been demonstrated that there are demyelinating plaques within the optic nerve.[43,44]

Conventional OCT imaging studies have demonstrated that the ganglion cell layer and the inner plexiform layer in MS individuals is significantly thinner compared to non-MS patients.[45] The extent of thinning of the inner retinal layers seems to reflect quite accurately the extent of the neurodegenerative processes occurring within the CNS.[45]

OCT-A findings in MS include significant reduction of the blood flow within the parafoveal region and the optic nerve head[17,20] (Figure 1). Lanzillo et al developed Expanded Disability Status Scale Scores.[19] The scores successfully correlated the thickness of the vascular network and the thickness of the inner retinal layers with the level of disability of MS patients.[19]

It is still not clear why the blood flow of the retina and optic nerve is reduced in MS patients. One postulated pathophysiological mechanism is that the death of the ganglion cell axons and subsequent reduction of retinal tissue volume lead to reduced metabolic demands and therefore reduced blood supply to the retina and optic nerve.[17,18] Another theory is that the inflammatory demyelinating process affects directly the integrity of the vascular endothelium of both the optic nerve and the retina, which results in reduced blood flow.[46] This is based on the fact that the cerebral and retinal vasculature exhibit very similar anatomy and physiology[14,15] and that MRIs of MS patients have demonstrated reduced blood flow within the grey and white matter.[47,48] However, this hypothesis has not been proven yet.

Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disorder which causes significant cognitive impairment and is the most common cause of dementia in the elderly population. The main histological feature is the gradual accumulation of an abnormally folded protein called beta-amyloid in the CNS.[21] There is a strong link between Alzheimer's, cardiovascular risk factors and reduced blood flow of the brain parenchyma.[49,50] Of note, it has also been observed that beta-amyloid protein can accumulate within the retina of patients that suffer

from Alzheimer's in a similar manner to the brain parenchyma.[51] Given these observations and the similarities of the retinal and cerebral vascular network, it has been postulated that the changes of the retinal vasculature in Alzheimer's patients could serve as a biomarker for the severity and progression of the disease.[7,52]

It is postulated that these changes are a consequence of the deposition of beta-amyloid plaques in the retina. The plaques apply compressive forces onto the retinal layers and but also the blood vessels, leading to reduced blood flow, hypoxia and lack of glucose and other nutrients, all of which are essential "fuel" for the highly metabolically active retinal cells.[21]

As a result, the hypoxic retina responds by producing vascular endothelial growth factors (VEGF) to promote angiogenesis and re-establish its blood supply. Nevertheless, the b-amyloid plaques prevent the process of angiogenesis, because they also form a mechanical barrier for the secretion of vascular endothelial growth factors (VEGF) confining them within the plaques and not allowing VEGF to reach adjacent healthy retina.[21]

The aforementioned pathophysiological mechanisms may be able to explain why some studies have found that the vascular density of the superficial and deep vascular plexus has been significantly lower in Alzheimer's patients compared to healthy controls.[21,23] In addition, the FAZ of Alzheimer's patients seems to be significantly compromised probably due to the compressive forces and the mechanical restriction posed on the retinal vascular network by the diffuse aggregation of b-amyloid plaques.[23]

As a consequence, the OCT-A demonstrates diminished blood flow that will eventually lead to thinning and death of retinal cells. It appears that the ganglion cell layer is more profoundly affected by the ischaemia, and the thinning and atrophy of the ganglion cell layer correlate quite well with the severity of Alzheimer's disease.[52]

Of note, only the vascular changes of the deep vascular retinal plexus seem to demonstrate a strong association with the loss of ganglion cell layer in Alzheimer's patients.[7] One proposed explanation is that the superficial vascular plexus is less sensitive to the accumulation of beta-amyloid plaques due to the larger size of its vessels compared to the deep plexus.[23]

Anterior Ischaemic Optic Neuropathy

Anterior ischaemic optic neuropathy can be divided in arteritic (AION) and non-arteritic (NAION). Arteritic suggests an inflammatory process within the lumen of the artery and the most common cause for this is giant cell arteritis. On the other hand, NAION is associated with cardiovascular risk factors such as hypertension, diabetes, hypercholesterolaemia.[27] OCT-A is able to show a reduction in the blood flow of the optic nerve head in both conditions but it cannot differentiate between the two[27] (Figure 2).

In NAION, it has been found that there is significant sectorial capillary density reduction and subsequent decrease in the blood flow to the corresponding region of the optic nerve head.[24,25] The extent of the loss of blood flow has been reported to correlate quite well with the amount of peripheral visual field loss and the reduction in visual acuity in NAION patients.[27,28] Macular hypoperfusion and significant thinning of the inner retinal layers (mainly the ganglion cell and inner plexiform layers) have also been described.[7,53]

LHON

This is a genetic disorder which is inherited via the maternal mitochondrial DNA. It affects mainly young males and presents initially with unilateral disc swelling and profound visual loss in the affected eye. After a few weeks or months, the fellow eye becomes involved and eventually both discs become pale and atrophic. The optic disc vessels are telangiectatic and they do not leak on fundus fluorescein angiography.[54] OCT-A reveals loss of peripapillary vessels and increased vessel tortuosity of the remaining ones, which leads to reduction in the blood flow of the optic nerve head and eventually to loss of nerve fibers and disc atrophy (Figure 3).

Disc Swelling Due to Raised Intracranial Pressure

True disc swelling due to idiopathic intracranial hypertension (papilloedema) or secondary to other causes may lead to a significant increase of the retinal nerve fiber layer (RNFL) thickness but also disruption of the inner layers.[55] In cases of papilloedema, there is inhibition of the axoplasmic flow along the axons of the ganglion cells within the inner retina and also aggregation of cellular debris.[56] On the other hand, pseudo-papilloedema of the optic disc does not demonstrate such histological features but ophthalmoscopically can resemble true oedema. Hence, it can be quite challenging to differentiate between the two clinical entities. Nevertheless, the distinction is mandatory, as true disc swelling may suggest an underlying condition that not only threatens the patient's sight but also his/her life. OCT and OCT-A may be quite

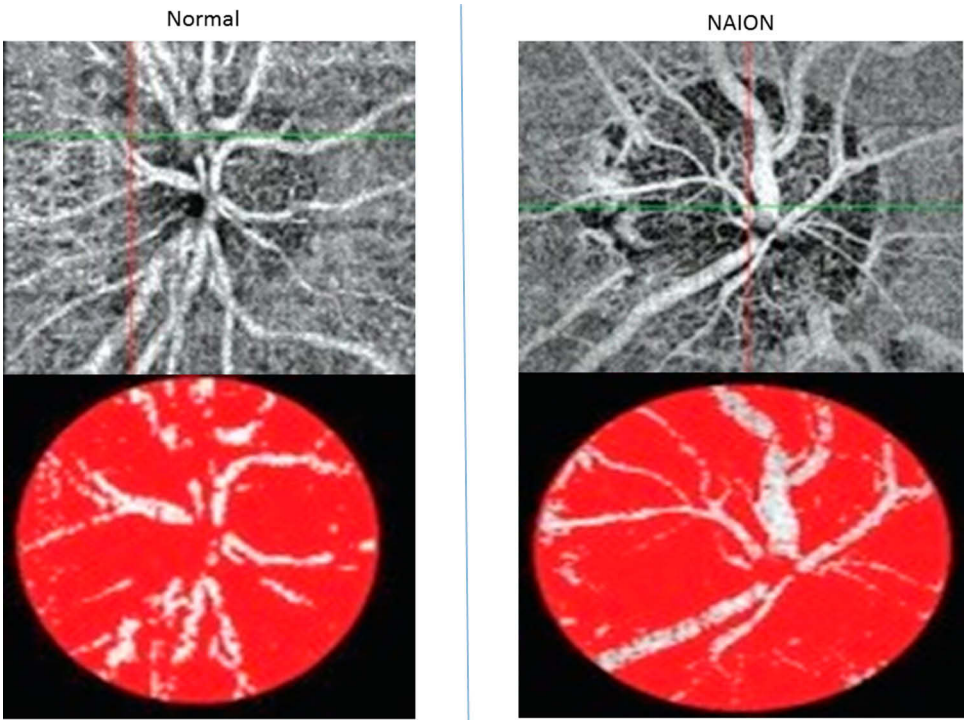

Figure 2 Upper left and lower left images demonstrate the appearance of a healthy optic disc. Upper right and lower right images demonstrate the attenuation and peripapillary capillary drop out of the optic nerve head vascular network in a patient with NAION.
Note: Copyright © 2017. International Journal of Ophthalmology. Modified from Ling JW, Yin X, Lu QY, Chen YY, Lu PR. Optical coherence tomography angiography of optic disc perfusion in non-arteritic anterior ischemic optic neuropathy. *Int J Ophthalmol*. 2017;10:1402–1406.[27]

valuable tools in order to distinguish between papilloedema and pseudo-papilloedema.

In papilloedema, the gangion cells that compose the inferior and superior quadrants of the optic nerve head are chiefly affected, because their axons are larger in caliper.[56–58] Carta et al demonstrated a statistically significant increase in the average RNFL thickness and in the RNFL thickness of the nasal quadrant of optic discs with papilloedema compared to discs with pseudo-papilloedema and also in healthy controls.[56]

OCT-A in a papilloedema case reported in literature has shown that there is increased vessel tortuosity and density along with increasing size of the affected vessels.[26] Furthermore, Fard et al demonstrated that OCT-A in papilloedema demonstrated increased whole image density and nasal peripapillary density compared to discs with pseudo-papilloedema.[59] This was particularly obvious in papilloedema grades 1 and 2.[59] In grade 3 or 4 papilloedema, the peripapillary capillary density was reduced and was not very useful to differentiate between grade 3 or 4 papilloedema from pseudo-papilloedema.[59] These observations were significant, as they suggest that OCT-A parameters can be of great value in cases where there is a diagnostic dilemma between early papilloedema and pseudo-papilloedema.[59]

Diabetic Retinopathy

Diabetic retinopathy was thought to be only a microvascular complication of diabetes. However, more recent studies have postulated that it is a more complex entity, where neurodegenerative changes may play a pivotal role,[60–67] especially during the initial stages of the disease.[64]

Numerous manuscripts have introduced the term neurovascular unit (NVU) in an attempt to describe the function of the blood-brain barrier (BRB).[64–67] Within the retina, the NVU represents an intimate communication between the neurosensory retinal cells (bipolar, horizontal, amacrine and ganglion cells), neuronal glial cells (Muller cells and astrocytes), vascular channels (endothelial cells and pericytes) and immune cells (macrophages).[64–67] The vascular network of the retina does not receive innervation from the autonomic nervous system, thus it is highly dependent on intrinsic regulatory mechanisms provided by the NVU which controls the blood flow within the retina.[68,69] Therefore, the NVU acts as a crucial homeostatic mechanism within the retina.

During the early stages of the disease, it appears that the homeostatic role of the NVU is compromised and this precedes the vascular changes.[60–67] These processes trigger

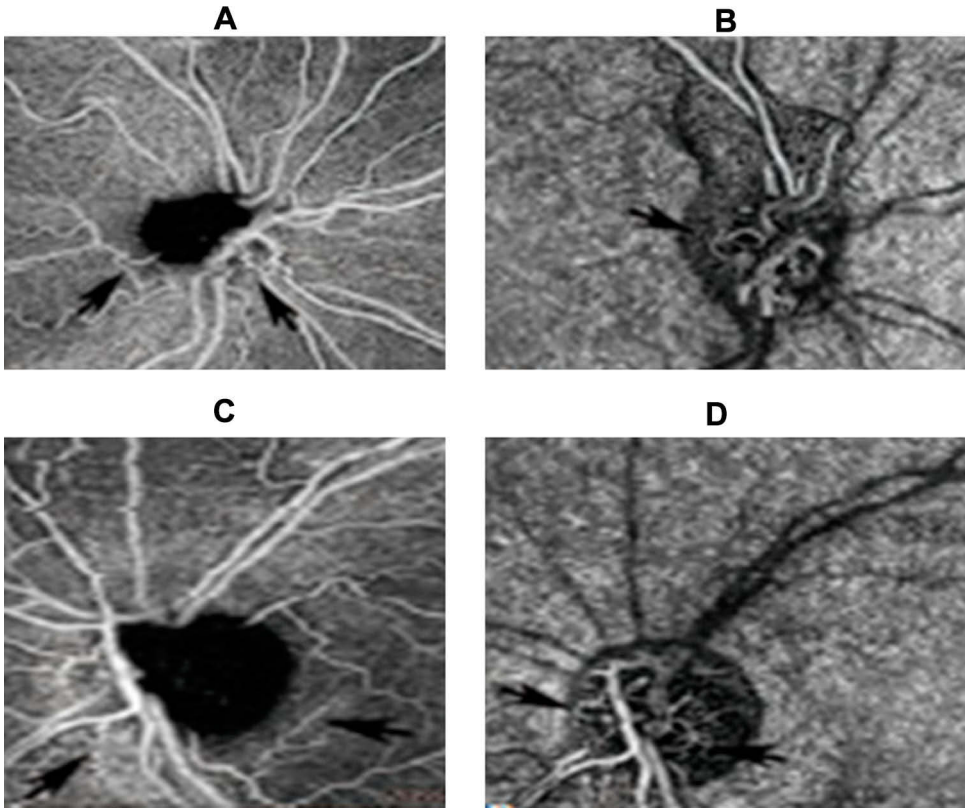

Figure 3 OCT-A images of a patient with Leber hereditary optic neuropathy.
Notes: (**A**–**C**) Peripapillary capillary telangiectatic vessels in the deep plexus shown with black arrows. (**B**–**D**) Peripapillary capillary telangiectatic vessels in the outer retina shown by black arrows. © 2016 Acta Ophthalmologica Scandinavica Foundation. Published by John Wiley & Sons Ltd. Modified from Takayama K, Ito Y, Kaneko H, Kataoka K, Ra E, Terasaki H. Optical coherence tomography angiography in leber hereditary optic neuropathy. *Acta Ophthalmol.* 2016;95(4):e344-e345.[54]

an increase in the extracellular concentration of glutamate and subsequent imbalance in the secretion of other neuroprotective factors within the retina.[60–67] As a result, there is increased reactive gliosis and neurosensory retinal cell apoptosis, which subsequently lead to low-grade inflammation, impaired haemodynamic response and disruption of the BRB. Eventually, the BRB break down will lead to the manifestation of microvascular impairment observed in diabetic retinopathy.[60–67] There are numerous neuroprotective factors that are implicated in the bridging between the neurodegenerative changes and the vascular changes.[60–67]

OCT-A can help identify vascular changes in diabetic patients, mainly microaneurysms and capillary drop out.[64,70] Of note, these changes can in fact be detected in diabetics prior to the manifestation of clinically evident diabetic retinopathy as seen in diabetic screening photographs or during slit-lamp examination.[71] In addition, these changes are more prominent in the deep capillary plexus that in the superficial.[71] The early detection of such changes on the OCT-A reflects the neurodegenerative processes occurring at the early stages of diabetic retinopathy. This important clue could be used as a biomarker for detecting changes before they become clinically evident and this can also be used as a guide to develop drugs which can have neuroprotective effect within the retina and prevent the appearance and progression of diabetic retinopathy.

Another important fact that needs to be highlighted is that there are studies suggesting that type 2 diabetics share similar pathophysiological pathways leading to retinal neurodegeneration with Alzheimer's disease.[72,73] Therefore, OCT-A in diabetics could potentially be useful as a screening tool for the identification in type 2 diabetics that are more vulnerable to develop cognitive impairment, which on its own may hinder the ability of these individuals to comply with lifestyle changes and treatment regimes.[64,72] Larger scale prospective studies, however, will be required to validate this hypothesis.

Parkinson's Disease and Its Variants

OCT has also been used to study the changes in the retinal layers and optic nerve in Parkinson's disease and its variants, which are Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA).[74–95]

Parkinson's disease is a disorder affecting the basal ganglia within the CNS, where dopamine is a very crucial neurotransmitter. Dopamine plays also a pivotal role within the retina regulating different visual processes. This is the reason why there were studies that tried to find a correlation between the changes between the RNFL thickness and the severity of the disease.

Altintas et al and Inzelberg et al described generalized RNFL thinning in patients with Parkinson's disease but there was no consensus between the two reports about the quadrants that were more profoundly affected.[75,76] RNFL thinning was confirmed by other reports in Parkinson's patients with both mild and severe disease.[74,77] Furthermore, there were reports that described the correlation between the extent of the RNFL thinning and the disease progression,[78,79] however this was disputed by two other reports.[80,81] Due to the controversial findings among the different reports, a meta-analysis was conducted to assess the validity of the different data and reported that there was RNFL thinning in all quadrants in parkinsonian patients.[82]

Another area of interest was the attempt to correlate the changes in the foveal area with the severity of Parkinson's disease. The results were controversial as with the RNFL thickness. In 2014, Garcia-Martin et al reported increased foveal thinning,[83] but a subsequent study by Shrier et al disputed the above finding.[84] The same study notably found a difference in the foveal thickness between the two eyes of the same patients that were included in that study.[84] Cubo et al described both increased foveal thinning and asymmetry in foveal thickness.[85] Another interesting finding of Cubo et al study was that the foveal thinning was more profound in the contralateral side of the more affected limb.[85] Finally, Spund et al suggested that patients with Parkinson's exhibit not only foveal thinning but also broadening of their foveal pit, which could potentially serve as a biomarker for the disease.[86]

Other studies also attempt to find a correlation between the severity of Parkinson's disease and the thickness of individual retinal layers. Albrecht et al described increased inner nuclear retinal layer thickness in individuals with Parkinson's disease.[87] Garcia Martin et al confirmed this but also reported thinning of the outer plexiform layer (OPL), inner plexiform layer (IPL), ganglion cell layer (GCL) and RNFL.[78] However, another study by Schneider et al disputed the above findings.[88]

One study focused on assessing the choroidal thickness in patients suffering from Parkinson's disease and reported that the choroidal thickness in such individuals was increased.[89] Nevertheless, more prospective studies are required to further validate this finding.

In addition to the above controversial findings, we also performed a literature search looking specifically for the use of OCT-A in Parkinson's disease and not only the conventional OCT. In a small prospective study, Kwapong et al reported reduced microvascular density in most areas of the whole retina.[90] In addition, the same report described strong correlation between the reduced vascular density of the superficial vascular retinal layer and the thinning of the inner plexiform and ganglion cell layers in patients suffering from Parkinson's disease.[90]

With regards to PSP, Albrecht et al reported generalized decrease in the total macular volume in PSP patients.[87] This finding was observed in a later study, which used OCT but also scanning laser polarimetry.[91] The same study also reported changes in parafoveal areas, reductions of the central minimum and thinning of the RNFL as measured by two devices, which were independent of disease severity and duration.[91] Schneider et al also suggested that PSP individuals exhibited increased thickness of their OPL with simultaneous thinning of the outer nuclear layer (ONL) compared to healthy controls.[88] Schneider et al further suggested that the OPL/ONL volume ratio was highly sensitive (91%) and specific (88%) in the distinction between PSP (<5.03) and MSA (>5.03).[88] However, we could not find any manuscripts mentioning the use of OCT-A specifically in PSP apart from the conventional disc OCT.

In MSA, a meta-analysis published in 2017 reported that there is a significant decrease in the RNFL thickness in the inferior, superior and nasal quadrant but less prominent in the temporal quadrant.[92] This means that the macular ganglion cell complex which is located at the temporal quadrant of the RNFL is less likely to be compromised.[92] These changes follow a completely different pattern from Parkinson's disease and therefore they can be used as a means of distinction between Parkinson's disease and MSA.[92] In addition, there have been two reports published prior to this meta-analysis suggesting a correlation of the RNFL thinning and disease severity in MSA patients.[93,94] Similarly, to PSP, despite our thorough and extensive search, we could not find any manuscripts mentioning the use of OCT-A specifically in MSA apart from the conventional OCT.

Despite the occasionally contradicting findings among the different studies as described above, it appears that OCT and OCT-A could evolve into useful tools in monitoring disease progression in the whole spectrum of

parkinsonian syndromes and also in differentiating between Parkinson's, PSP and MSA.

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare autosomal dominant condition attributed to Notch-3 mutations.[96] It is characterized by the aggregation of osmiophilic material within the brain vasculature, thickening of the vessel wall and lumen stenosis.[97] It is the most common hereditary cause for ischaemic strokes manifesting at an average age of 49.[98] In the absence of other cardiovascular risk factors, CADASIL is considered a genetic model to understand small vessel disease.[99]

Due to the morphological similarities between the retinal and the brain vasculature, studies have focused on studying the changes observed in the retinal vascular network and how these can be linked to the alteration of cerebral blood flow in CADASIL patients. The first report was released in 2014 by Alten et al, where conventional OCT was used.[99] The study demonstrated increased RNFL thickness due to increased retinal vessel diameter, thickened venous lumina and reduced arterial lumina.[99] The choroidal vessels were unaffected.[99] These findings were in consensus with previous histological findings.[100] However, assessment of the retinal blood flow or the optic nerve head with OCT-A was not done, as OCT-A was not FDA approved until 2015. However, it was the first study that attempted to use multimodal imaging to assess morphological features of the retinal vasculature in CADASIL individuals and compare those with healthy controls. Fang et al confirmed these observations and found a link between retinal vessel changes and changes detected on MRI scans of such patients.[101]

After the FDA granted approval for the use of OCT-A in 2015, the same study group assessed the macular retinal and optic nerve head blood flow and choriocapillaris blood flow in CADASIL individuals with OCT-A.[98] The study suggested a reduction in the blood flow of the deep retinal vein plexus of the macula, but the blood flow of the optic nerve head, choriocapillaris and the superficial vascular plexus were not affected.[98] The study group attributed these changes to the loss of pericytes occurring due to the Notch-3 mutations.[98] However, the blood flow changes did not lead to clinical symptoms of impaired visual function. The same study tried to correlate the OCT-A findings with the MRI brain findings in such patients. However, the study did not find any correlation between the MRI FLAIR sequence findings and the OCT-A findings.[98] To date, this is the only study that used OCT-A for the study of the retinal vasculature in CADASIL individuals.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis known also as "Lou Gehrig's Disease" is a rare neurodegenerative disorder that affects both the lower and upper motor neurons.[102] A few studies attempted to use conventional OCT to investigate the involvement of the optic nerve and whether this could be used as a biomarker for the early detection of ALS. There were reports that suggested RNFL thinning,[103–108] however these observations have been disputed by other study groups.[109,110]

All the above studies yielded contradictory results because they were cross-sectional without follow-up results and also included ALS patients with different clinical manifestations, different stages of disease severity.[111] Rojas et al performed a prospective study with early ALS patients to assess the OCT findings in baseline visit and after a 6 month follow-up.[111] The results suggested an increased thickness of the inner macular ring temporally and inferiorly compared to healthy controls, progressive RNFL thinning after 6 months of follow-up and a moderate correlation between the OCT findings and the severity of the disease.[111] However, the follow-up period was relatively short and the number of eyes was also small.

None of the above reports and studies used specifically the OCT-A to assess blood flow of the macular region or the optic nerve in ALS patients. Some of these reports were published prior to 2015, when OCT-A received FDA approval for use in everyday clinical practice. Others published after the approval did not look into the retinal and optic nerve blood flow. Larger scale longitudinal prospective studies need to be conducted with both conventional OCT and OCT-A to elucidate more robust data. The general consensus is that OCT and OCT-A have the potential of becoming valuable tools in the early detection and monitoring of ALS patients.[112]

Huntington's Disease

This is another rare inherited fully penetrant neurodegenerative disorder leading to personality changes, dementia and chorea.[113]

In our research, we found 3 papers describing the OCT findings in patients with Huntington's disease.[114–116] Again, the reports refer to conventional OCT and no OCT-A imaging was utilized to assess the blood flow of

the retina and the optic nerve head. The reports suggest temporal and superior RNFL thinning compared to healthy controls and also reduced macular thickness.[114–116] As with ALS, these are small sample cross-sectional studies and larger scale prospective longitudinal studies with the implementation of both conventional OCT and also OCT-A must be conducted to obtain more reliable data.

Wolfram Syndrome

A study by Asanad et al assessed the use of OCT-A in patients with Wolfram syndrome, rare neurodegenerative disease including diabetes insipidus, diabetes mellitus, deafness, and optic neuropathy.[117,118] The OCT-A demonstrated reduced blood flow of the radial peripapillary capillary plexus (RPC) and superficial capillary plexus (SCP), which correlated well with the corresponding RNFL thinning.[118] The authors postulate a mitochondrial involvement related to the observed OCT-A findings.[117,118]

Lesions of the Visual Pathway

In another case-control observational study, Parozanni et al used both conventional OCT and OCT-A to assess optic nerve and macular changes between 26 patients suffering from optic nerve axonal degeneration secondary to posterior optic pathway glioma involving the chiasma, the postchiasmatic visual pathway, or both (but not involving optic nerves) and 24 gender- and age-matched healthy participants.[119] The study demonstrated markedly reduced RNFL thickness between the patients and the control group.[119] Macular deep capillary plexus (DCP) and RPC were also reduced and the reduction correlated with the observed corresponding RNFL thinning.[119] SCP perfusion did not demonstrate statistically significant differences between the two groups.[119] The authors suggest that the compressive lesions lead to the death and loss of axons, which reduced retinal metabolic demands and subsequently lead to vascular remodeling and reduced blood perfusion and they postulate that the Muller cells may be the culprit for this cascade of events.[119]

Migraines

There have been also reports to assess the use of OCT-A and its ability to detect vascular changes in the retina of patients with migraines with aura and without aura.[120,121] Chang et al described that patients with migraine with aura exhibited enlarged foveal avascular zone (FAZ), reduced parafoveal SCP blood flow and reduced RPC superiorly compared to those without aura and also compared to healthy controls.[120] The authors did not observe any changes in OCT-A of patients with migraine without aura and healthy controls.[120] They postulate that these findings may make patients with migraines with aura more prone to retinal vascular occlusion, ischaemic optic neuropathies and normal tension glaucoma.[120]

Ulusoy et al agreed with the findings of the above study about patients suffering with migraines with aura, but in their study, they also observed changes in the blood flow in the macular and optic nerve region in patients without aura as well.[121] The authors also tried to correlate these findings with white matter hyperintensities observed in the MRI brain of patients with migraines with and without aura.[121] The authors observed there was a statistically significant correlation of the OCT-A findings and the MRI findings only in the migraine with aura group.[121]

A study published in April 2020 looked at patients with migraines without aura.[122] The study reported no statistically significant difference between the patient group and the control group with regard to ganglion cell complex, foveal, and retinal nerve fiber layer thicknesses.[122] In addition, the study reported no statistically significant differences in the superficial or deep vascular perfusion densities of the optic disc between the groups. Furthermore, this study contradicted the findings of Chang et al, as the migraine without aura group exhibited a statistically significant enlargement of the FAZ and reduced macular blood flow compared to the healthy controls.[122] The migraine without aura group was further divided into two subgroups, one with white matter hyperintensities and one without.[122] There was no significant difference concerning the FAZ size or vascular densities between the migraine groups.[122] The authors acknowledge that their study was a small sample cross-sectional study and has limitations and they are in the process of conducting a follow-up study to investigate further.[122]

In summary, the published manuscripts about the use of OCT-A in the assessment of the retinal and optic nerve perfusion have yielded contradictory results for the same reason as for other aforementioned conditions. They are cross-sectional studies with small sample sizes and therefore larger scale prospective longitudinal studies with the implementation of both conventional OCT and also OCT-A must be conducted to obtain more reliable data.

Limitations in the Use of OCT-A

Since OCT-A was introduced in 2015, the current data available about its applications stem from studies that contain small sample sizes and this limits the level of evidence and the validity of the findings.[123] There is still

a significant learning curve in terms of interpretation and there is no unanimous protocol as to which parameters should be taken into account and this may lead to false-positive or -negative results that affect the validity of the findings and yield contradictory results among different study groups.[117]

Another important limitation is that many of these neurodegenerative disorders can affect the mental capacity of such patients and subsequently their cooperation when OCT-A images are obtained. As a result, this may lead to poor quality images that can lead to inaccurate interpretation due to motion artifacts.[123] Since OCT-A demands high levels of patient cooperation and attentiveness, it may not be quite useful imaging tools in children due to their very short attention span.[117] Furthermore, the commercially available OCT-A devices are not able to provide a wide field of view of the vasculature of the peripheral retina and the views are very limited to the posterior pole.[123] This prevents us from studying meticulously the whole retinal periphery and this has also led to numerous studies that are confined to the macular and optic nerve head regions so far. In addition, not all amount of light can be transmitted through the erythrocytes and this mainly affects the precise depiction of the choroidal vasculature, since the melanosomes of the retinal pigment epithelium not only absorb but also induce light scattering.[117]

Another important limitation is that many of these patients usually are elderly and they may suffer from other conditions such as hypertensive retinopathy, diabetic retinopathy, primary open-angle glaucoma, vein occlusions and macular degeneration. The OCT-A findings in retinal vascular disease have a significant amount of overlapping with the retinal changes induced by the neurodegenerative disorders and therefore it is quite challenging to describe accurately the real extent of the contributions of each pathological entity due to substandard segmentation carried out by the current OCT-A software available.[123] In the same context, other macular or optic nerve lesions, such as epiretinal membranes or myelinated nerve fiber layers can obscure the images obtained by the OCT-A devices.[117,123]

Finally, the size of the retinal capillaries varies from 5μm to 10 μm. These numbers are at the lower levels of the transverse resolution of the OCT-A beams and this might affect the calculations of the vessel density.[123]

Conclusion

In summary, we advocate that OCT-A can play a pivotal role in the detection and monitoring of a wide range of neurodegenerative disorders. OCT-A can provide valuable data about the structural changes of the retinal and optic nerve vascular network and this can be used for the development of biomarkers to monitor the disease progression and also to develop potential future treatments which could halt or reverse the progression of such diseases that are currently incurable. However, there are many shortcomings which prevent the wider use of OCT-A for the above purposes. Larger prospective longitudinal studies will need to be conducted in order to optimize the quality of the OCT-A images and the accurate interpretation of the data.

Disclosure

The authors report no conflicts of interest in this work. The authors alone are responsible for the content and writing of the paper.

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