LITERATURE REVIEW

ROLE OF OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY (OCTA) IN ANTERIOR ISCHEMIC OPTIC NEUROPATHY

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ABSTRACT

Introduction: *Anterior ischemic optic neuropathy (AION) is the most common type of optic neuropathy with symptoms of sudden and painless visual field defect and vision loss. Although evaluating the nonperfusion areas of the vascular ischemia have traditionally been visualized through fluorescein angiography, OCTA has proven to be effective in noninvasively representing the retinal vascular network. This literature review aims to evaluate the quantitaive OCTA assessment of peripapillary vessel density (VD) changes in AION.*

Methods: *Literature search was performed in four databases (PubMed, ScienceDirect, ProQuest, and Cochrane Library) from 2018 to 2022 to identify relevant articles. Five studies were included in this review.*

Results: *All five studies on OCTA findings of NAION eyes reported a reduction in the vessel density of peripapillary capillary plexus when compared to either the healthy control eyes or the fellow unaffected eyes. OCTA reveals vascular changes in both forms, aiding prognosis and treatment. One study comparing NAION and AAION indicates reduced vessel density in NAION and AAION, with more severe abnormalities and reduction of vessel density in AAION.*

Conclusion: *OCTA can visualize alterations in vascular density in both types of AION, AAION and NAION, with a notably more pronounced reduction in peripapillary vessel density observed in AAION.*

Keywords: *anterior ischemic optic neuropathy, optical coherence tomography angiography, peripapillary vessel density*

INTRODUCTION

Anterior ischemic optic neuropathy (AION) is the most common type of optic neuropathy that affects elder people. AION includes both arteritic and non-arteritic forms[1,2] 90% of AION cases are Non-arteritic AION (NAION) with an annual incidence of approximately 10.3 per 100,000 individuals and a median age of 72, more commonly affecting males and whites. It is characterized by sudden and painless visual field defect and vision loss. Examination of the fundus typically reveals ONH edema at the acute stage, which could be diffuse or segmental, and resolves over 6-11 weeks, then replaced by disc pallor. Although the underlying mechanism of NAION remains unknown, the available evidence reveals that it may

be associated with perfusion deficiency of optic nerve head (ONH) microcirculation that is predominantly supplied by the short ciliary arteries. Probable risk factors that increase the onset includes hypertension, hypercholesterolemia, diabetes mellitus, nocturnal hypotension, and obstruction sleep apnea.[3,4] Arteritic AION (AAION), on the other hand, which occurs most commonly in association with giant cell arteritis (GCA), a large vessel vasculitis occurring in people older than 50, since it is the most common manifestation of end-organ ischemia in GCA (up to 20% of patients). It is caused by inflammatory and thrombotic occlusion of short posterior ciliary arteries (PCA).[3,4] Nerve fibers from the optic nerve head travel through the lamina cribrosa into the extraocular space. The optic nerve then gets a myelin sheath covering just posterior to the sclera. From then on, it traverses through the orbital apex into the intracranial space, where the right and left optic nerve cross each other at the optic chiasm and ending its journey at the visual cortex of the occipital lobe. The optic nerve may experience ischemia anywhere along this route.[4]

Optical coherence tomography angiography (OCTA) is a noninvasive, rapid, and simple imaging modality that provides a 3-dimensional image of the structural and microvascular information of the posterior pole of the retina in vivo. It was first made commercially available in 2014. This technology was developed as an extension of optical coherence tomography (OCT) imaging and utilizes motion contrast to detect blood flow. When two successive images are taken, stationary objects will appear the same, while moving objects will change. OCTA captures successive A-scans of the same retinal location, with each scan capture separated by a brief lapse in time, hence there will be a difference in the signals detected between the two scans due to motions happening between the scans. This difference in the detected signals is termed decorrelation signal. Since the retina is a static structure, the decorrelation signal is caused by the movement of blood throughout the retinal vasculature, and thus enabling the generation of a decorrelation map that mirrors the blood flow and represents the vascular networks in the back of the eye. Traditionally, nonperfusion areas are visualized through fluorescein angiography and indocyanine green angiography, but OCTA allows representation of the retinal vascular network especially peripapillary blood supply noninvasively without the need for contrast dye administration. Since the recent development of OCTA, this technique has been used in several fields in ophthalmology inculding in AION. [5,6]

It is only recently that OCTA is vastly studied in optical neuropathy, with various and sometimes contradicting results. Moreover, its role in the evaluating vessel density in AION has yet to be established. This literature review aims to evaluate the OCTA assessment of peripapillary vessel density (VD) and optic nerve head flow changes found in AION patients.

METHODS

Literature search was done in four online databases (PubMed, ScienceDirect, ProQuest, and Cochrane Library) from 2018 to 2022. Search terms such as "arteritic anterior ischemic optic neuropathy", "non-arteritic anterior ischemic optic neuropathy", "optical coherence tomography angiography", "OCTA", along with other relevant synonyms and derivatives were included (Table 1). The search was then limited to articles with full text availability and English as the publication language.

Based on search results in the previous section, articles were considered eligible to be reviewed if these inclusion criteria are met: (1) Subjects were patients diagnosed with AION; (2) Studies included the evaluation of OCTA as a diagnostic tool in AION cases; (3) Study outcomes include peripapillary vessel density and optic nerve head flow area. On the other hand, exclusion criteria were studies not written in English, conducted in non-human subjects, not applying OCTA, inaccessible full text, and articles in form of editorial publication. The flow of literature search was reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). All reviewed studies were rated based on the Oxford Center of Evidence-Based Medicine 2011 Level of Evidence on diagnostic studies.[7] As this review highlights cross-sectional studies, validity assessment of selected articles will be conducted with Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2). Information extracted from each study includes the following: authors, publication year, the location and year in which the study is conducted, study design, number of subjects involved, variables examined, and outcome data.

RESULTS

The search term used in the previous chapter resulted in 153 studies. 5 duplicates were then removed and a total of 148 studies were screened based on their respective titles and abstracts. 131 articles were excluded because of unmet inclusion criteria or irrelevant outcomes for this literature review. Full-test review was then done on the remaining 17 articles, excluding 12 articles. In total, 5 articles were included in this review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart on Figure 1 illustrates the process of article selection.

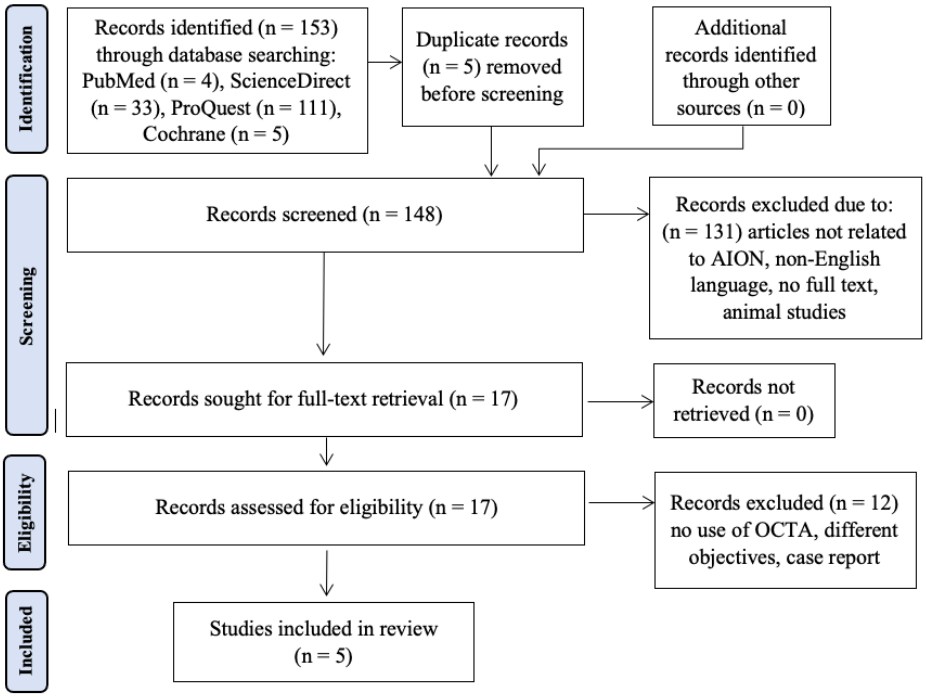

Figure 1. PRISMA flow chart

A total of 5 studies, ranging from 2018-2022, reporting outcomes of 236 eyes were included in this review. Two of the included studies were cross-sectional observational studies (Haitham et al[12], Pierro et al[14]), achieving a Level II Evidence based on the Oxford Center of Evidence Based Medicine (OCEBM). The other studies consisted of retrospective cohort studies (Liu et al[15]) retrospective comparative case series (Gaier et al[11]), and prospective comparative observational study (Aghdam et al[13]), hence the level of evidence assessment according to OCEBM was not applicable (N/A). Three of the studies (Gaier et al[11], Haitham et al[12], Liu et al[15]) compared OCTA findings in eyes with non-arteritic anterior ischemic optic neuropathy (NAION) with unaffected fellow eyes, and three among the studies (Haitham et al[12], Aghdam et al[13], Pierro et al[14]) also comparing OCTA findings with the eyes of healthy controls. One studies compared NAION eyes with AAION eyes (Pierro et al[14]). When it comes to the study outcomes, all studies reported that eyes with optic neuritis showed either microvascular impairment in comparison to fellow unaffected eyes or healthy controls, or progressively worsening microvascular impairment over time. The summary of the studies' characteristics is presented in Table 1

Table 1. Overview of the included studies

Author (Year)	Study Design (Level of Evidence)	Year Conducted	Country	Types of Diseases	Number of Subjects	Gender (M/F)	PDP
Gaier et al[11] (2018)	Retrospective comparative case series (N/A)	2016-2017	United States	NAION	25 eyes (7 acute and 18 non-acute) in 19 patients with NAION, 6 unaffected fellow eyes	19/5	Ac & chr
Haitham et al[12] (2020)	Cross-sectional observastional study (II)	2020	Egypt	NAION	25 eyes with unilateral acute NAION, 25 unaffected fellow eyes used as a control group	14/11	Ac
Aghdam et al[13] (2018)	Prospective comparative observational study (N/A)	2016-2017	Iran	NAION	10 eyes with ONHD, 10 eyes with NAION, and 10 normal eyes	4/6	Ac
Pierro et al[14] (2020)	Cross-sectional observational study (II)	2020	Italy	NAION & AAION	15 eyes with AAION & 15 eyes with NAION, 15 healthy controls	9/6 & 8/7	Ac
Liu et al[15] (2020)	Retrospective cohort study (N/A)	2017-2019	China	NAION	21 eyes with NAION & 19 unaffected fellow eyes	12/9	Ac & Chr

AAION: arteritic anterior ischemic optic neuropathy; Ac: acute; Chr: chronic; M: male, F: female, N/A: not available; NAION: non-arteritic anterior ischemic optic neuropathy, PDP: patient disease phase

Table 2. presents the demographics of the patients in the included studies. The mean age of the NAION patients involved is 47 years and above. Gender distribution of the patients are also quite heterogenous, with the male/female ratio ranging from 4/6 up to 19/5. OCTA devices across the studies are also variable, with a total of four different kinds of devices.

Table 2. Demographics of the patients in the included studies

Study	Age (Mean ± SD)	Gender (M/F)	OCTA Device
Gaier et al[11]	58.71 ± 13.19	19/5	Optovue, Zeiss
Haitham et al[12]	60.2 ± 3.5	14/11	Optovue
Aghdam et al[13]	56.80 ± 6.81	4/6	Optovue
Pierro et al[14]	47.7 ± 11.35	8/7	Topcon
Liu et al[15]	54.67 ± 7.55	12/9	Optovue
Lee et al[16]	63 ± 11	14/7	Heidelberg

N/A: not available; OCTA: optical coherence tomography angiography; SD: standard deviation; M: male; F: female

Findings on vessel density of the peripapillary capillary is shown on Table 3. All studies unanimously reported reduction of both vessel densities in patients with NAION at the various fields examined by OCTA. Peripapillary vessel density values highest in the study by Aghdam et al[13], which is 49.47 ± 5.42.

Table 3. Vessel density findings from each study

Study	Peripapillary VD (WMD or mean ± SD)
Gaier et al[11]	N/A
Haitham et al[12]	Whole: 44.7 ± 2.1 (p<0.001) Inside: 42.9 ± 3.5 (p<0.001) Superior: 42.1 ± 2.4 (p<0.001) Inferior: 43.7 ± 1.8 (p<0.001) Nasal: 46.1 ± 3.3 (p<0.001) Temporal: 47.6 ± 2.9 (p<0.001)
Aghdam et al[13]	49.47 ± 5.42 (p<0.001)
Pierro et al[14]	AAION vs NAION: 37 ± 1 vs 40 ± 1 (p<0.01)
Liu et al[15]	Whole baseline: 46.32 ± 2.63 Whole 1-2 weeks: 44.29 ± 3.28 Whole 1-2 months: 41.45 ± 3.43 Whole 3-6 months: 38.22 ± 4.00

N/A: not available; SD: standard deviation; WMD: weighted mean difference; VD: vessel density

In the study by Gaier et al[11] (Figure 2), there was a 4-5-fold greater amount of major retinal vessels in the superficial lamina in comparison to the superficial capillaries of the unaffected eyes, both at the disc and peripapillary. There were also more amounts of patent capillary vessel density in the peripapillary area compared to the papillary area in the unaffected eye and acutely affected eye ($p < 0.005$), but not for non-acutely affected eyes ($p = 0.745$). Quantitative analysis showed that there was a significant reduction in the angiographic signal from acutely affected eyes in comparison to the unaffected eyes in the papillary and peripapillary regions ($p < 0.022$). The difference in the major vessel density between non-acutely affected and unaffected eyes was not statistically significant ($p > 0.209$) in both sampling regions.

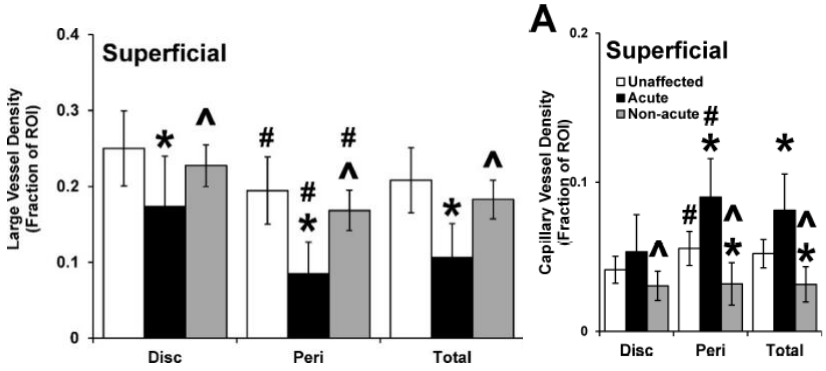

Figure 2. Quantitative analysis results of OCTA data and comparison in unaffected, acutely affected, and non-acutely affected eyes[11]

Only one study (Pierro et al[14]) analyzed the difference between AAION and NAION. 15 eyes of 15 AAION patients, 15 eyes of 15 NAION patients and 15 eyes of healthy controls were evaluated. OCTA quantitative analysis from this study revealed significant differences between patients and control. VD values for RPC and SCP for AAION and NAION eyes showed significant differences compared to controls ($p<0.01$). VD value were significantly lower both in AAION and NAION eyes compared to contralateral and control eyes ($p<0.01$).

DISCUSSION

OCTA is a non-invasive imaging modality that can provide three-dimensional visualization of perfused vasculature of the retina and choroid. In addition to the ability of optical coherence tomography (OCT) to analyze the intensity of the reflected light, OCTA is also able to analyze the temporal changes of the OCT signal based on repeated OCT section images from the same location of the retina. Through this method, it is possible to separate the temporal signal changes due to moving particles (i.e., erythrocyte flow through the blood vessels) from other possible causes of signal change such as noise in the OCT signal or eye

motion. As it is non-invasive, OCTA is regularly seen superior to fluorescein angiography. But this seems not to be the case, since FA and ICGA are able to display dynamic phenomena namely dye leakage, pooling, and staining, that are not observable with OCTA because they involve no blood cells in motion. Though this phenomena are useful in clinical diagnosis, retinal pathology can sometimes be obscured by hemorrhage or leakage, hence the ability of OCTA to generate high definition images of the microvasculature are able to work hand in hand with the information provided from dye-based angiography.[17]

AION is a term used to describe optic neuropathies due to a transient or permanent interruption of the optic nerve blood supply in any of its portion. AIONs are basically classified into AION and NAION.[1,2,3,4] This review explored the role of OCTA as a diagnostic tool for AION. From a total of the five studies screened in this review, all studies discussed the role of OCTA in patients with non-arteritic anterior ischemic optic neuropathy (NAION), with one study also discussing AAION. The availability of OCTA have enabled the identification of early and late structural changes in the retina and optic nerve head, therefore may assist the prediction of visual outcomes and the expansion of knowledge regarding the pathogenesis, also the development of more effective medical interventions.[18]

NAION is also one of the ischemic differential diagnoses of optic disc edema, along with inflammatory and papilledema. Patients with this disease typically report sudden onset of painless vision loss, and hallmarks signs include decreased visual acuity and/or visual field loss along with a relative afferent pupillary defect (RAPD) on the affected side (if the fellow eye is normal). The occurrence of optic disc edema at the acute phase of NAION is thought to be from ischemia due to hypoperfusion of the small vessels supplying the anterior portion of the optic nerve. This acute swelling of the disc may progress in the first 2-3 weeks after symptom onset and will start to remit by 6 weeks. In time, the optic disc becomes pale, either partly or globally.[18,19]

Arteritic anterior ischemic optic neuropathy, on the other hand, is most frequently caused by giant-cell arteritis (GCA) and often results in more severe visual loss. In contrast to NAION, OCT has not been extensively used in AAION, both in acute or chronic phases. With OCTA, findings of AAION are similar to NAION, showing defects of the radial peripapillary capillary (RPC).[18] Both NAION and AAION are characterized by the presence of optic nerve ischemia and inflammation, in which both contributed to the manifestation of symptoms like visual acuity reduction and visual field defects.

The relatively novel non-invasive OCTA has allowed the quantitative assessment of the circulation peripapillary and retinal vessels in different ophthalmic diseases. OCTA provides

useful information on the ongoing vascular impairment of AION. To be exact, remarkable perfusion reductions have been identified, and also localized and well-matched to the area of visual field defects.[14]

Several studies have reported the results of peripapillary OCTA in NAION eyes, both in the acute and post-acute stages. Those studies reported both a reduced radial peripapillary capillary (RPC) density in acute NAION and a progressive reduction of vessels within 3 months. Another study has also shown flow impairment in the RPC corresponds to structural OCT deficits of the peripapillary retinal nerve fiber layer (p-RNFL) in 80% of eyes.[18] These are in sync with the findings of this review, in which all studies on OCTA findings of NAION eyes reported a reduction in the vessel density of peripapillary capillary plexus when compared to either the healthy control eyes or the fellow unaffected eyes.

Peripapillary vessel density loss in post-acute NAION has also been reported in other studies, but this does not necessarily mean that OCTA directly displays the optic nerve ischemia in NAION. This is because NAION is known to be resulted from acute infarction of the retrolaminar segments of the optic nerve head, which are primarily sourced from the short posterior ciliary arteries. The current technology of OCTA is not yet able to show those deep-located vessels. Another reason is that the location of decreased peripapillary vessel density in post-acute NAION is similar to the locations of defected visual field and also correlates with the severity of p-RNFL thinning. This information indicates that RPC reduction (RPC dropouts) is not specifically due to NAION, and that p-RNFL loss may have also contributed. NAION patients are more prone to have diabetes, hypertension, and even sleep apnea, which is another possible cause of RPC reduction.[18,19]

The study by Pierro et al discovered the presence of vascular tortuosity together with reduced vessel density in AAION eyes, which was significantly more severe in comparison to NAION eyes, particularly in terms of vessel density (VD) for RPC and SCP ($p<0.01$). Quantitative analysis by OCTA has displayed more vascular abnormalities in AAION than NAION, which is expected since AAION is characterized by more optic disc swelling. However, further studies are still needed to determine quantitative values as possible cut-offs to distinguish AAION from NAION eyes.[14,20]

CONCLUSION

In conclusion, this review demonstrated that OCTA can display vascular density changes, mainly showing a reduction in peripapillary vessel density thickness in cases of AION both arteritic and non-arteritic which was found significantly more severe in AAION than

NAION. On the other hand, though the methodology of this review is thorough, the studies included presents different limitations and should not be ignored, and the risk of bias and variability of data collected should be regarded meticulously. Further study is recommended to assess differences regarding vascular impairment in AION.

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