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Original Article

# Optic Nerve Head Microvascular Changes Associated with Intracranial Aneurysms

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## Abstract

**Objectives:** The aim of our study is to report optic nerve head (ONH) microvascular changes secondary to intracranial saccular aneurysms, evaluated by optic coherence tomography angiography.

**Methods:** A prospective study was conducted on consecutive intracranial saccular aneurysm patients who underwent neurosurgical intervention and consulted for ophthalmic evaluation at the post-operative period. Comprehensive ophthalmic evaluation, including best-corrected visual acuity, manifest refraction, color vision, pupillary light reflexes, intraocular pressure, slit-lamp biomicroscopy, fundoscopy, and investigation of the function of cranial nerves, was performed. Demographical and clinical data of eyes with intracranial aneurysm (Group 1) were compared to those of age-matched controls (Group 2). In patients with unilateral intracranial aneurysm, microvascular indices of the ipsilateral eye were also compared with those of the contralateral eye.

**Results:** Twenty-eight eyes of 16 patients in Group 1 and 32 eyes of 16 age-matched healthy controls in Group 2 were included in the study. In Group 1, only 1 patient was diagnosed incidentally, whereas the remaining 15 patients were diagnosed after subarachnoid hemorrhage (SAH). ONH microvascular indices were similar in both groups ($p>0.05$). Both vascular density and thickness were decreased at the nasal inferior sector of ONH in Group 1, compared to Group 2; however, these differences were statistically insignificant. In Group 1, 8 patients have unilateral intracranial aneurysm. Microvascular indices at the ipsilateral eye were statistically insignificantly increased compared to those at the contralateral eye of patients with unilateral intracranial aneurysm.

**Conclusion:** Intracranial saccular aneurysms, associated SAH, or neurosurgical intervention did not seem to cause any significant change in ONH microvascular indices. Further studies with a larger sample size and evaluating intracranial aneurysms located in different anatomical regions will contribute to the interpretation of the present results.

**Keywords:** Intracranial aneurysm, microvascular indices, optic coherence tomography angiography, optic nerve head, subarachnoid hemorrhage

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## Introduction

Intracranial saccular aneurysms are acquired arterial outpouchings that affect about 2–5% of the general population. They are often diagnosed at the 50s, with male predominance (2:1). Although the aneurysms are usually isolated and sporadic, 15% of cases might be familial. There are some predisposing factors, including Marfan syndrome, Ehler-Danlos syndrome, pseudoxanthoma elasticum, polycystic kidney disease, coarctation of the aorta, fibromuscular dysplasia, neurofibromatosis, sickle cell anemia, arteriovenous malformations, Behçet's disease, and moya-moya disease. Intracranial aneurysms are mainly located at the branching points of major arteries, most commonly at the internal carotid artery, middle cerebral artery, and circle of Willis (1,2). Most intracranial aneurysms remain asymptomatic until they rupture. Unruptured intracranial aneurysms are often diagnosed incidentally on brain magnetic resonance angiography or computed tomography angiography. Whereas spontaneous rupture of an intracranial aneurysm leads to subarachnoid hemorrhage (SAH), which has a high mortality rate. The size and location of an aneurysmal sac are independent predictors of future rupture (1,3).

To date, there is plenty of literature pertaining the intraocular hemorrhages in the retina and macula regions, and oculomotor cranial neuropathies secondary to intracranial lesions (2,4-6). However, neuronal and microvascular alterations at the optic nerve head (ONH) are sparsely evaluated. The aim of our study is to report ONH microvascular changes secondary to intracranial saccular aneurysms, evaluated by non-invasive, fast, and repeatable optic coherence tomography angiography (OCTA).

## Methods

A prospective study was conducted at the Ophthalmology and Neurosurgery Departments between February 2020 and February 2021. The study was approved by the Institutional Review Board (Date: 16 January 2020; No: 11-12-20) and was conducted according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient or patients' guardian before enrollment.

The patients diagnosed with intracranial aneurysms in the Neurosurgery Department were enrolled in the study and consulted for ophthalmic examination. The patients who were admitted with acute SAH due to ruptured intracranial aneurysms were examined at the post-operative period. All neurosurgical interventions were performed by the same surgeon (I.D.).

Patients with a Glasgow Coma Scale score of 15/15 were included in the study. The eyes with an intraocular pressure >20 mmHg, severe cataract or media opacities, history of glaucoma, retinal artery or vein occlusion, diabetic retinopathy, or spherical equivalent worse than −3.0 D were excluded from the study to avoid any potential bias due to ONH changes. Patients who are unable to cooperate on ophthalmic examination or imaging were excluded from the study.

All of the patients were interviewed regarding their medical history and underwent a comprehensive ophthalmic evaluation, including best-corrected visual acuity, manifest refraction, color vision, pupillary light reflexes, intraocular pressure, slit-lamp biomicroscopy, fundoscopy, and investigation of the function of cranial nerves 3, 4, and 6. Cranial neuropathies were determined based on: presence of ptosis, diplopi, restriction of ocular movements, and/or anisocoria.

Microvascular changes were evaluated by OCTA. The images were obtained using RTVue XR Avanti spectral domain-optical coherence tomography (Optovue Inc., Fremont, California, USA). A split-spectrum amplitude decorrelation algorithm demonstrated erythrocyte motion-dependent angiography (7), with an A-scan rate of 70,000 scans/s (wavelength = 840 nm, bandwidth = 45 nm) and 400 × 400 A-scans per B-scan, a 4.5 mm × 4.5 mm cube centered onto the ONH. Numerical data about vessel density and thickness were evaluated for the whole image, disc, and peripapillary region using the flow density mapping software AngioAnalytics. Microvascular measurements in eyes with intracranial aneurysm (Group 1) were compared to those of age-matched controls (Group 2). In patients with unilateral intracranial aneurysm, microvascular indices of the eye on the ipsilateral side of the aneurysm were also compared with those of the eye on the contralateral side of the aneurysm.

The primary outcome measure was the ONH microvascular changes in eyes with intracranial saccular aneurysms, in comparison with those of controls. Secondary outcome measures were neuroophthalmological and fundoscopic findings in those eyes.

### Statistical Analysis

Data were described as mean±standard deviation for numerical and frequency (percentage) for categorical variables. Normality of the data was tested using the Kolmogorov–Smirnov test and the Shapiro–Wilk test. Nominal variables were compared with Chi-square or Fisher's Exact test, whereas numerical variables were compared with Independent Samples t-test or Mann–Whitney U test as appropriate. Numerical variables of ipsilateral and contralateral eyes of patients in Group 1 were compared with related samples Wilcoxon Signed Rank test. Statistical analyses were performed with the Statistical Package for Social Sciences Version 26.0, Chicago, IL. The level of statistical significance was set at $p<0.05$.

## Results

During the study time interval, 30 patients underwent intracranial aneurysm surgery and responded to the study invitation. Only in 32 eyes of 18 patients' quality of OCTA imaging was more than 6/10. Among them, 28 eyes of 16 patients fulfilled the inclusion criteria and were included in Group 1, whereas Group 2 composed of 32 eyes of 16 age-matched healthy controls.

Clinical and demographic features of Group 1 were demonstrated in Table 1. Only 1 patient was diagnosed incidentally, whereas the remaining 15 patients were admitted to the hospital with SAH. All of the cases had anterior small or medium-sized saccular aneurysms located in the anterior circulation, and they were treated with the microsurgical clipping technique (Fig. 1). Ophthalmic evaluation was performed at the post-operative period in all cases, after a mean interval of 5.0±4.5 (3.9; 0.1–16.8) months between the neurosurgical intervention and ophthalmological examination. The frequency of hypertensive cases was similar in both groups (p=0.075), whereas males were predominant in Group 1, compared to Group 2.

ONH microvascular indices evaluated with optic disc OCTA were similar in both groups (Table 2).

In Group 1, 8 patients had unilateral intracranial aneurysm. Among them, both vascular density and thickness of ONH at all quadrants were increased in ipsilateral eyes, compared to those of contralateral eyes. However, these differences were statistically insignificant (Table 3).

**Table 1.** Clinical and demographical features of intracranial aneurysm cases

| | |
|---|---|
| Age (years) | 49.9±12.5 (53.0; 22–69) |
| Sex (M:F) | 11:5 |
| Hypertension | 5 (31.3%) |
| Max diameter of aneurysm (mm) | 7.68±3.02 (7.50; 3–13) |
| Size of aneurysm | <10 mm: n=10 (62.5%) |
| | ≥10 mm: n=6 (37.5%) |
| | Small (<7 mm): n=8 (50.0%) |
| | Medium (7–14 mm): n=8 (50.0%) |
| | Large (15–24 mm): n=0 |
| | Giant (≥25 mm): n=0 |
| Site of aneurysm | ACoA: n=5 (31.3%) |
| | ICA: n=1 (6.3%) |
| | MCA: n=4 (25.0%) |
| | ACA: n=1 (6.3%) |
| BCVA (decimals) | 0.98±0.07 (1.0;0.7–1.0) |

Values are presented as Mean±Standard deviation for numerical and frequency (%) for categorical variables. BCVA: Best-corrected visual acuity; AcoA: Anterior communicating artery; ICA: Internal carotid artery; MCA: Middle cerebral artery; ACA: Anterior cerebral artery.

In Group 1, none of the patient's eyes revealed ptosis, diplopia, anisocoria, relative afferent pupillary defect, papiledema, optic atrophy, or Terson syndrome during ophthalmological evaluation. In 2 eyes of 2 patients, there were peripapillary hemorrhages and hypertensive retinopathy findings. In 1 eye of another patient, visual acuity was measured as light perception and projection, and exotropia was present. Since the OCTA imaging of could not be performed adequately, this eye was excluded from the study. In both eyes of another patient, color vision was 1/16 and his medical history revealed congenital color blindness.

## Discussion

In eyes with intracranial saccular aneurysm, ONH microvascular indices, evaluated by OCTA, were found to be comparable to those of controls. Although statistically insignificant, there was an asymmetry between the ipsilateral eye and the contralateral eye among patients with unilateral aneurysm, and ONH vessel density and thickness were both increased at the ipsilateral eye. Peripapillary hemorrhages and hypertensive changes were the most commonly encountered ocular pathologies in eyes with intracranial saccular aneurysms, whereas ocular motor nerve palsies (third, fourth, or sixth cranial nerves) or Terson Syndrome were not seen in any of our patients' eyes. Other neuroophthalmological complications secondary to increased intracranial pressure or intracranial surgery were not encountered in any patient's eyes.

Intracranial saccular aneurysms are expected to affect ONH microvascular structures in many ways. Primary damage to optic nerve or its vasculature by the aneurysmal sac (8,9), underlying vascular or endothelial pathology (10), hypoperfusion of ophthalmic artery (11), and increased intracranial pressure, orbital venous pressure or vasospasm due to SAH (4,12) could be the possible mechanisms for the ONH microvascular alterations. Besides, any compressive or ischemic damage of intracranial visual pathways, such as the optic chiasm, lateral geniculate body, Meyer's loop, and optic radiation, might result in retrograde damage of the optic nerve (4,13), and thereby decreased microvascularity on OCTA (14). Both unruptured and ruptured intracranial saccular aneurysms might initiate these alterations. However, compressive damage to the posterior visual pathway is usually produced by large or giant aneurysms (15). In our study population, none of the aneurysms appeared to compress the posterior visual pathway or was of a substantial size. On the other hand, ONH microvasculature was evaluated at the post-operative period in all cases. Theoretically, in sur-

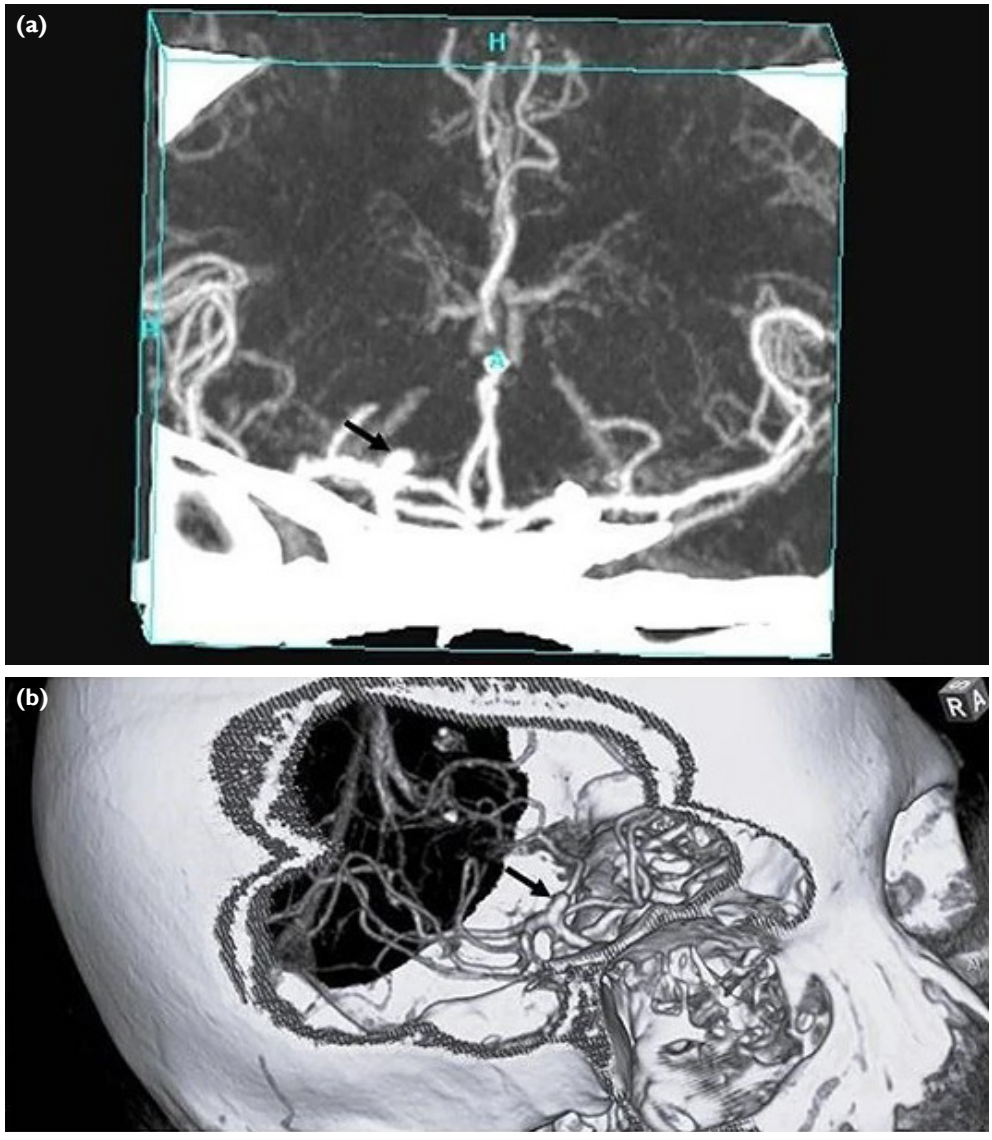


**Figure 1.** Preoperative computerized tomography angiography **(a)** and 3-dimensional reconstruction **(b)** revealed saccular aneurysm (arrow) on the right internal carotid artery.

gically treated aneurysms, optic nerve damage could have been originated from surgical manipulation around the nerve or from interactions between its vasculature and the extravasated blood (16,17). Although uncomplicated microsurgical clipping of an aneurysm could be performed in all cases, our small sample size might still lead to underestimation of those possible alterations on ONH. Nevertheless, among patients with unilateral intracranial aneurysm, microvascular indices of ONH were increased at the ipsilateral eye, compared to those of contralateral eyes. Although this asymmetry was statistically insignificant, alterations at ONH might be attributed to the SAH, leading to increased intracranial pressure, optic nerve compression, and venous congestion.

Previously, Albanna et al. (18) evaluated retinal vessel density of aneurysmal SAH patients to assess intracranial vascular alterations and cerebral autoregulation. The authors performed Dynamic Vessel Analyzer (Imedos Systems UG, Jena) in awake and cooperated patients and reported 93.3% (14/15) satisfactory image quality (18). In our study, although OCTA imaging was performed in awake patients after the acute phase of SAH and after surgical repair when the Glasgow Coma Scale score was 15/15, only 19/30 patients were able to cooperate for imaging. Besides, there were plenty of patients who underwent intracranial aneurysmal clipping in our neurosurgery department, but were immobile at the early post-operative period. Although OCTA imaging has been introduced relatively recently, it has gained a wide range of use in ophthalmology practice. Its non-invasive nature, safety, repeatability, and high-resolution image quality make OCTA imaging usually the first choice for the diagnosis and follow-up of various vascular diseases of the retina or optic disc (19-21). However, our outcomes indicate

**Table 2.** Optic nerve head microvascular indices in study groups

| | Group 1 | Group 2 | P |
|---|---|---|---|
| Vascular density | | | |
| Whole | 50.20±4.57 | 50.55±2.169 | 0.917 |
| Inside | 49.43±7.20 | 49.08±4.73 | 0.200 |
| Peripapillary | 53.23±4.45 | 53.08±2.74 | 0.614 |
| Superior hemi | 53.65±4.43 | 53.15±2.98 | 0.403 |
| Inferior hemi | 52.71±4.69 | 52.99±2.82 | 0.830 |
| Nasal superior | 51.19±6.74 | 50.93±3.42 | 0.314 |
| Nasal inferior | 48.95±7.03 | 50.50±3.82 | 0.472 |
| Inferior nasal | 51.62±7.33 | 51.53±4.38 | 0.614 |
| Inferior temporal | 58.51±4.39 | 57.60±5.06 | 0.733 |
| Temporal inferior | 53.32±5.66 | 53.08±4.06 | 0.680 |
| Temporal superior | 55.55±4.77 | 55.15±3.01 | 0.417 |
| Superior temporal | 57.59±4.87 | 55.32±10.20 | 0.616 |
| Superior nasal | 51.46±5.03 | 50.61±4.48 | 0.267 |
| Thickness | | | |
| Peripapillary | 113.46±11.71 | 113.28±13.96 | 0.818 |
| Superior hemi | 112.30±11.96 | 114.38±14.87 | 0.982 |
| Inferior hemi | 114.14±13.13 | 112.19±13.79 | 0.853 |
| Nasal superior | 108.769±16.09 | 112.19±17.66 | 0.563 |
| Nasal inferior | 91.68±12.66 | 94.78±13.47 | 0.386 |
| Inferior nasal | 144.21±27.02 | 134.63±19.29 | 0.257 |
| Inferior temporal | 147.54±18.69 | 148.34±27.57 | 0.481 |
| Temporal inferior | 72.41±13.28 | 71.19±12.25 | 0.714 |
| Temporal superior | 73.26±10.38 | 73.64±11.50 | 0.932 |
| Superior temporal | 130.04±17.82 | 136.19±20.42 | 0.263 |
| Superior nasal | 141.52±24.19 | 138.94±30.19 | 0.460 |

Values are presented as Mean±Standard Deviation. P: Independent Samples t-test or Mann–Whitney U test.

**Table 3.** Comparative evaluation of ipsilateral and contralateral optic nerve head microvascular indices in patients with intracranial aneurysm

| | Ipsilateral eye | Contralateral eye | p |
|---|---|---|---|
| Vascular density | | | |
| Whole | 50.12±4.64 | 47.76±6.76 | 0.397 |
| Inside | 50.79±9.02 | 49.43±8.68 | 0.672 |
| Peripapillary | 53.194.83 | 50.54±6.00 | 0.345 |
| Superior hemi | 53.15±4.81 | 51.31±6.24 | 0.917 |
| Inferior hemi | 52.99±5.30 | 49.71±5.83 | 0.128 |
| Nasal superior | 49.80±4.44 | 46.76±10.51 | 0.866 |
| Nasal inferior | 49.24±6.28 | 43.57±10.20 | 0.091 |
| Inferior nasal | 52.08±7.09 | 47.40±10.42 | 0.310 |
| Inferior temporal | 57.39±4.97 | 56.13±3.15 | 0.735 |
| Temporal inferior | 54.74±5.58 | 53.97±2.55 | 0.753 |
| Temporal superior | 56.23±5.41 | 54.29±1.96 | 0.674 |
| Superior temporal | 57.29±5.60 | 56.83±5.10 | 0.833 |
| Superior nasal | 51.11±5.89 | 49.66±7.21 | 0.500 |
| Thickness | | | |
| Peripapillary | 111.56±9.59 | 106.86±12.81 | 0.833 |
| Superior hemi | 109.50±9.04 | 105.14±14.99 | 1.000 |
| Inferior hemi | 111.78±9.52 | 108.29±10.75 | 0.916 |
| Nasal superior | 106.22±12.87 | 99.00±18.67 | 0.176 |
| Nasal inferior | 89.11±11.41 | 81.71±12.70 | 0.400 |
| Inferior nasal | 133.00±15.07 | 128.57±16.36 | 0.866 |
| Inferior temporal | 143.67±15.14 | 149.86±17.04 | 0.397 |
| Temporal inferior | 79.25±9.95 | 78.14±10.24 | 0.892 |
| Temporal superior | 77.88±7.445 | 73.86±12.86 | 0.600 |
| Superior temporal | 126.75±17.00 | 126.71±30.18 | 0.345 |
| Superior nasal | 132.75±18.45 | 127.71±20.89 | 0.752 |

Values are presented as Mean±Standard Deviation. P: Related samples Wilcoxon Signed Rank test.

that there are still a need for portable, easy-to-use, and fast diagnostic devices in ophthalmology, especially for diseases with neurological components or for inpatients.

Due to the common underlying etiology, structural alterations may take part in ONH vasculature before the development or clinical diagnosis of intracranial aneurysm. In this prospective study, we expected to find out some ocular vascular abnormalities for the prompt recognition of intracranial aneurysms before rupture to prevent its devastating complications. In addition, we would like to investigate possible correlations between the ONH vasculature and some features of intracranial aneurysms, such as its form (fusiform or saccular) or its size (micro- or macroaneurysm). However, we were not able to find out any significant change in ONH microvascular indices or its fundoscopic appearance. Still, further studies may elucidate possible similar vascular abnormalities of the optic nerve, retina, and choroid that are part of the central nervous system, in association with intracranial aneurysms.

Among the limitations of this study is the small sample size. Therefore, some noticeable differences could not be demonstrated as being statistically significant. Furthermore, our sample does not represent the whole scale of SAHs or the topographical organization of aneurysms. No posterior circulation aneurysm was included since they are almost always treated with endovascularly. Another apparent lim-

itation might be the fact that virtually no data on the ophthalmic status of patients before the SAH were available to us. None of our measurements could be done at the pre-operative period. Therefore, the effect of intracranial surgery or SAH on ONH microvasculature could not be eliminated.

## Conclusion

In cases with intracranial saccular aneurysm, aneurysmal sac, SAH, or neurosurgical treatment did not seem to cause any significant change in ONH microvascular indices. Studies to be conducted in cases of intracranial aneurysms located in different anatomical regions will contribute to the interpretation of the present results. We believe that our study will lead to further prospective studies with a large number of patients in the future.

### Disclosures

**Ethics Committee Approval:** The study was approved by the Institutional Review Board (Date: 16 January 2020; No: 11-12-20) and was conducted according to the tenets of the Declaration of Helsinki. Written informed consent was obtained.

**Peer-review:** External peer-reviewed.

**Conflict of Interest:** None declared.

**Use of AI for Writing Assistance:** Not declared.

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