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CASE SERIES

Insights into Ocular Emergencies: case Series on Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) Secondary to Acute Angle Closure Glaucoma

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Abstract: This case series aims to report the manifestation of acute secondary optic neuropathy attributed to optic nerve injury associated with a singular episode of markedly elevated intraocular pressure (IOP) during an acute glaucoma attack. The correlation between acute primary angle-closure (APAC) and non-arteritic anterior ischemic optic neuropathy (NAION) remains uncertain within the context of current knowledge. Definitive conclusions regarding the causal relationship between APAC and NAION or their mutual influence cannot be established based on the current evidence. The association between these conditions is recognized as a potential link, and comprehensive research is imperative to elucidate their interrelationship thoroughly. This case series emphasizes the importance of promptly addressing acute optic nerve injury and neuropathy associated with elevated intraocular pressure (IOP) in patients with crowded disc anatomical risk factors. It underscores the need for proactive interventions to prevent irreversible damage, highlighting the infrequent yet vision-compromising occurrence of non-arteritic anterior ischemic optic neuropathy (NAION) in acute primary angle-closure (APAC).

Keywords: AACG, NAION, Acute Glaucoma Attack, Neuropathy

Introduction

An acute angle-closure (AAC) episode occurs when the peripheral iris obstructs the trabecular meshwork, leading to a sudden and significant increase in intraocular pressure (IOP), with the potential for irreversible vision impairment if not promptly addressed.[1,2] Post-acute phase, optic nerve responses may vary, including minimal changes, typical glaucomatous cupping, or pallor with reduced retinal nerve fiber layer (RNFL) and minimal cupping.[2]

Non-arteritic anterior ischemic optic neuropathy (NAION) ranks as the second most prevalent optic neuropathy,[3] with a higher incidence in older individuals.[4] Characterized by optic nerve ischemia due to hypoperfusion of short posterior ciliary arteries (SPCAs), NAION results in sudden, painless, unilateral vision loss. Optic disc edema, whether segmental or diffuse, may be observed without apparent arteritis, often linked to arterial hypertension, nocturnal hypotension, obstructive sleep apnea (OSA), and diabetes mellitus. The pathogenesis involves hypoperfusion of the posterior ciliary arteries of the optic nerve head (ONH), leading to ischemia and subsequent pallor, reduced RNFL thickness, and minimal cupping post-resolution.[5,6]

Interestingly, some patients, post-AAC resolution, exhibit a pale optic disc with minimal cupping, resembling post-optic nerve insult, including NAION. This similarity in post-AAC outcomes may partially be explained by the impact of

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IOP on ocular perfusion, where an elevation of approximately 50 mmHg in IOP correlates with a decline in inner retinal capillary density.[7,8] The presented case series, featuring three cases of simultaneous bilateral AAC and NAION, offers a compelling illustration of the intricate relationship between IOP dynamics and ocular perfusion, resulting in acute secondary optic neuropathy due to optic nerve injury induced by a sudden increase in intraocular pressure during a glaucoma attack.

Case Presentation

Case 1

A 48-year-old female patient was referred to our clinic with a diagnosis of a history of acute glaucoma attacks in the right eye (IOP: 62mmHg) that occurred 2 weeks ago. The patient presented with complaints of pain, blurred vision, and red eyes. This was the first time such symptoms were experienced by the patient. Initially, the patient received oral acetazolamide 500mg, timolol ED, and dexamethasone ED as treatment.

On ophthalmological examination, the best-corrected visual acuity (BCVA) was 0.9 in the right eye and 1.0 in the left eye. The intraocular pressure (IOP) was measured at 15mmHg in the right eye and 19mmHg in the left eye. Pupils were dilated, and sluggish, RAPD was inconclusive and glaucomflecken was observed in the right eye (Figure 1A and B). The cornea appeared relatively clear, the anterior chamber was narrow, and mild sclerotic cataracts were found in both eyes. Gonioscopy examination revealed peripheral anterior synechiae (PAS) in all quadrants of the right eye (Figure 2) and Shaffer grade 2 in all quadrants of the left eye. Examination of the posterior segment showed optic disc edema in the right eye (Figure 3).

Due to the presence of optic disc edema in the right eye, an optical coherence tomography (OCT) examination of the optic nerve head (Figure 4) and anterior segment (AS-OCT) (Figure 5) was performed. The Humphrey visual field test (Figure 6A and B) revealed significant visual defects in the inferior arcuate region of the right eye, with a significant increase in neuroretinal thickness and retinal nerve fiber layer (RNFL) consistent with optic disc edema (Figure 7). In the fellow eye, the optic disc appeared to be crowded with a cup-to-disc ratio (CDR) of 0.1–0.2 (Figure 4).

Therefore, the patient was diagnosed with acute angle-closure glaucoma with concomitant non-arteritic anterior ischemic optic neuropathy (NAION) in the right eye. As the patient's IOP was stable, it was decided to perform a laser peripheral iridotomy (LPI) in both eyes. The deepened anterior chamber was visualized in both eyes. The patient was also prescribed latanoprost/timolol maleate to stabilize IOP and pentoxifylline for managing NAION. Risk factor assessments were further conducted. The neurological assessment yielded no remarkable findings. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, and aggregation markers were all normal. Brain and orbit magnetic resonance imaging (MRI) showed no abnormalities. Blood examinations revealed elevated total cholesterol and LDL levels.

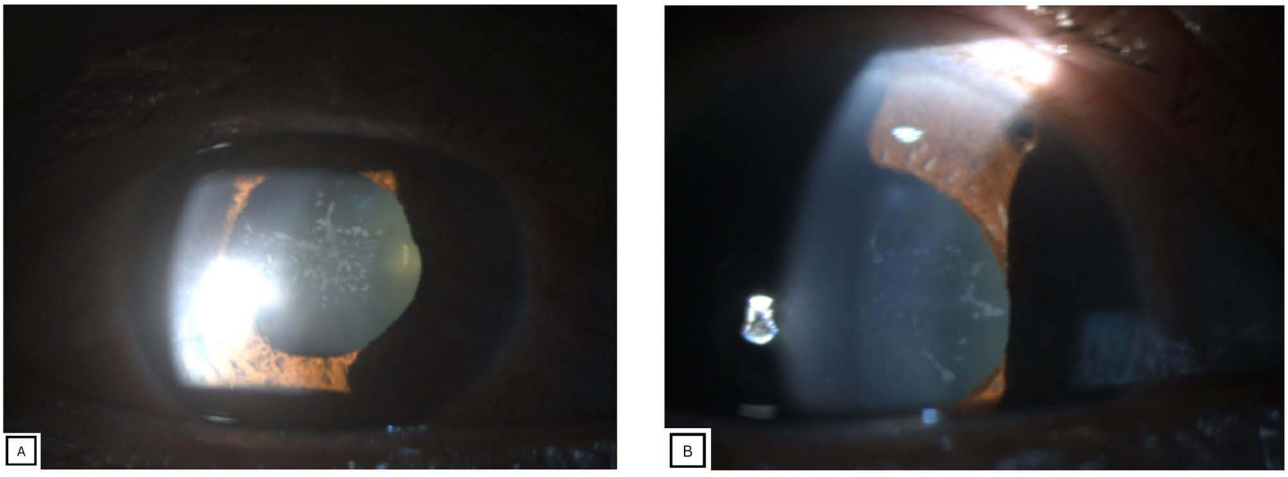

Figure 1 (**A**)Dilated pupil in the right eye, glaucomflecken, and (**B**) patent peripheral iridectomy in the right eye.

Figure 2 Peripheral anterior synechiae visualized by gonioscopy.

Figure 3 Fundus photography of (**A**) right eye; swollen optic nerve head and (**B**) left eye; normal optic nerve head.

After two weeks, the IOP reduced to 12 mmHg in the right eye and 15mmHg in the left eye, BCVA in both eyes was 1.0, with a patent peripheral iridectomy, and optic disc edema was resolved.

Case 2

A 58-year-old female patient presented with complaints of pain in her left eye, sudden blurred vision, and accompanied by nausea and vomiting for the past 2 weeks. The patient denied having a history of hypertension, diabetes, or hypercholesterolemia. These complaints were experienced for the first time. The patient's uncorrected visual acuity (UCVA) was measured at 0.5 and 0.10, while best-corrected visual acuity (BCVA) was 1.00 and 0.10 in the right and left eyes, respectively.

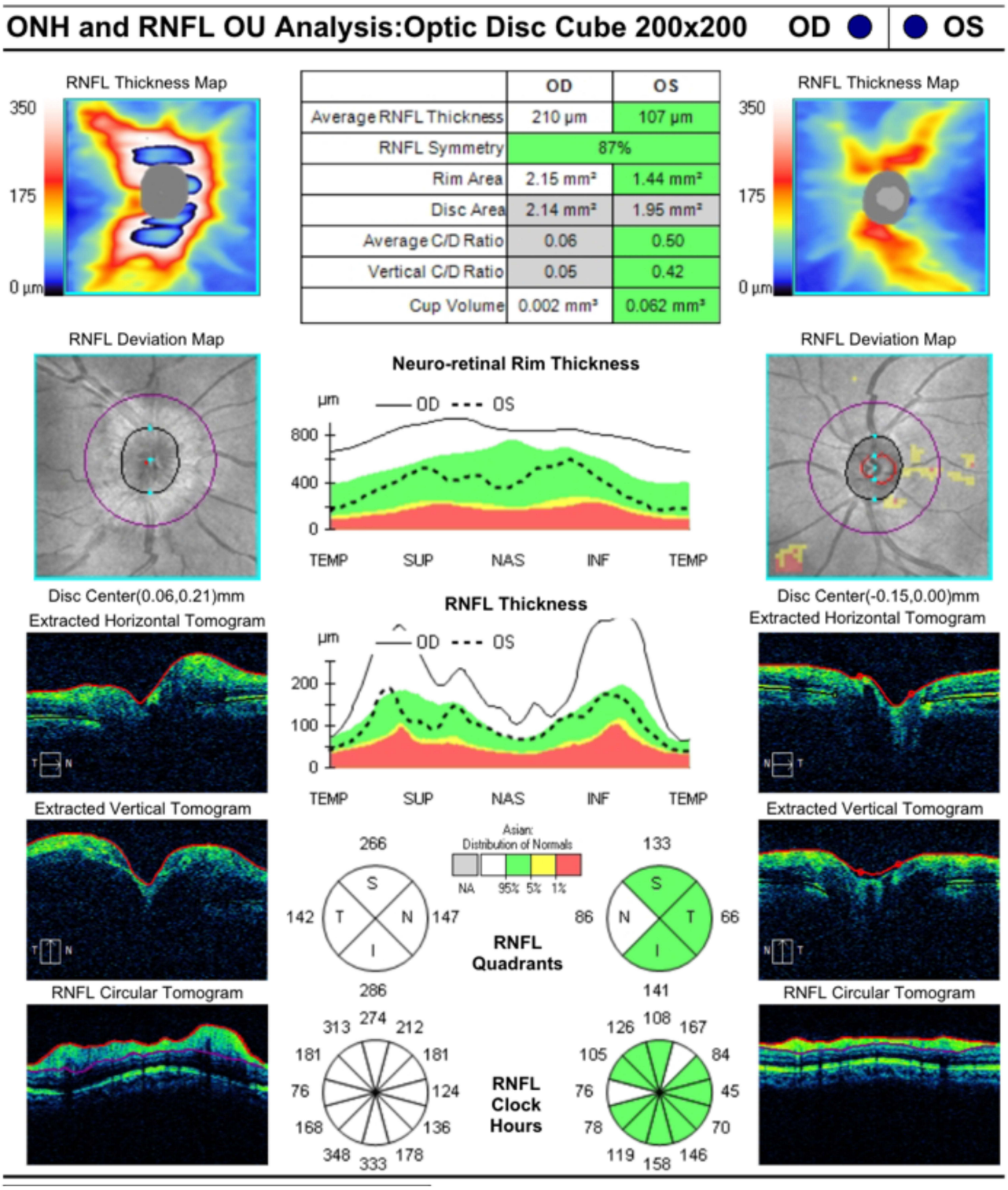

Figure 4 OCT of the ONH in the RE and LE was conducted. The optical coherence tomography (OCT) of the optic nerve head revealed that the analysis of the retinal nerve fiber layer showed 360° optic nerve edema in the right eye, while no optic nerve edema was detected in the left eye, with a small crowded cup-to-disc ratio (CDR).

Intraocular pressure (IOP) examination using applanation tonometry showed readings of 16 mmHg in the right eye and 63 mmHg in the left eye. The pupil was dilated with glaucomflecken appearance, and there was a moderate relative afferent pupillary defect (RAPD) in the left eye. The left eye exhibited ciliary injection, significant corneal

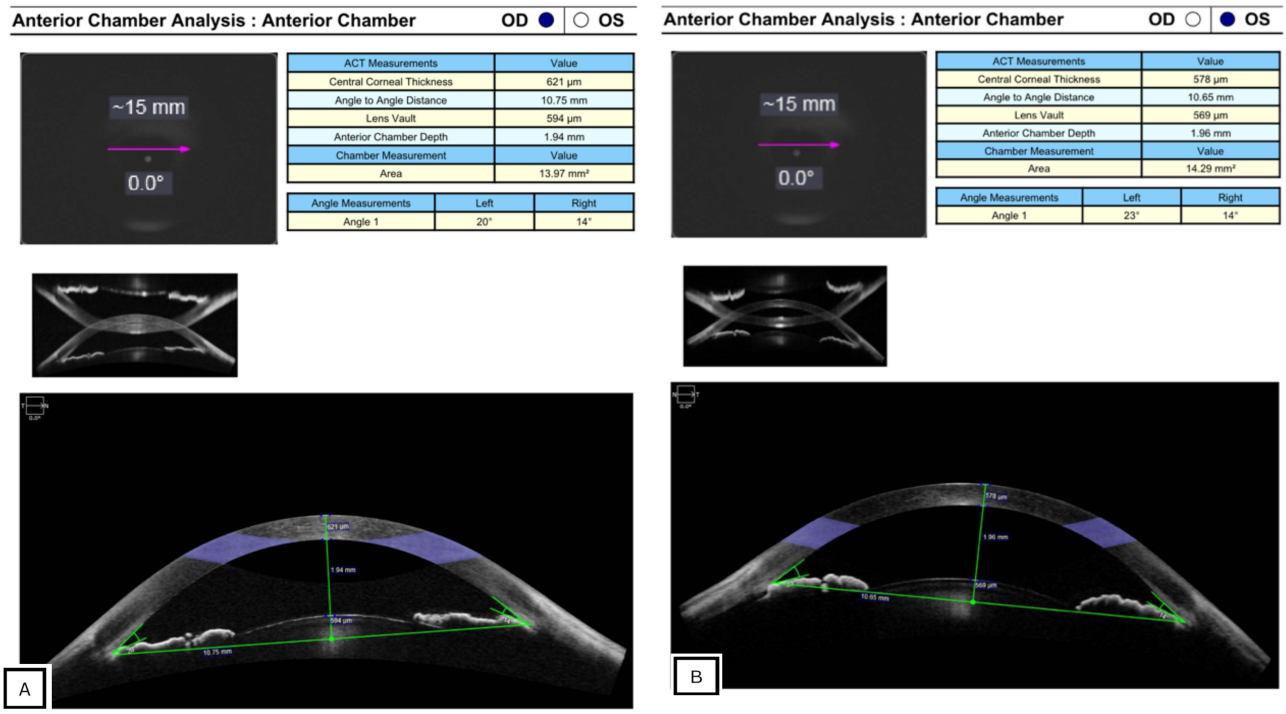

Figure 5 AS-OCT on the RE and LE. The anterior chamber angles in both eyes exhibited similarity, with both being shallow. Pink arrows in the ACT imaging showed the plane where the calculations were taken.

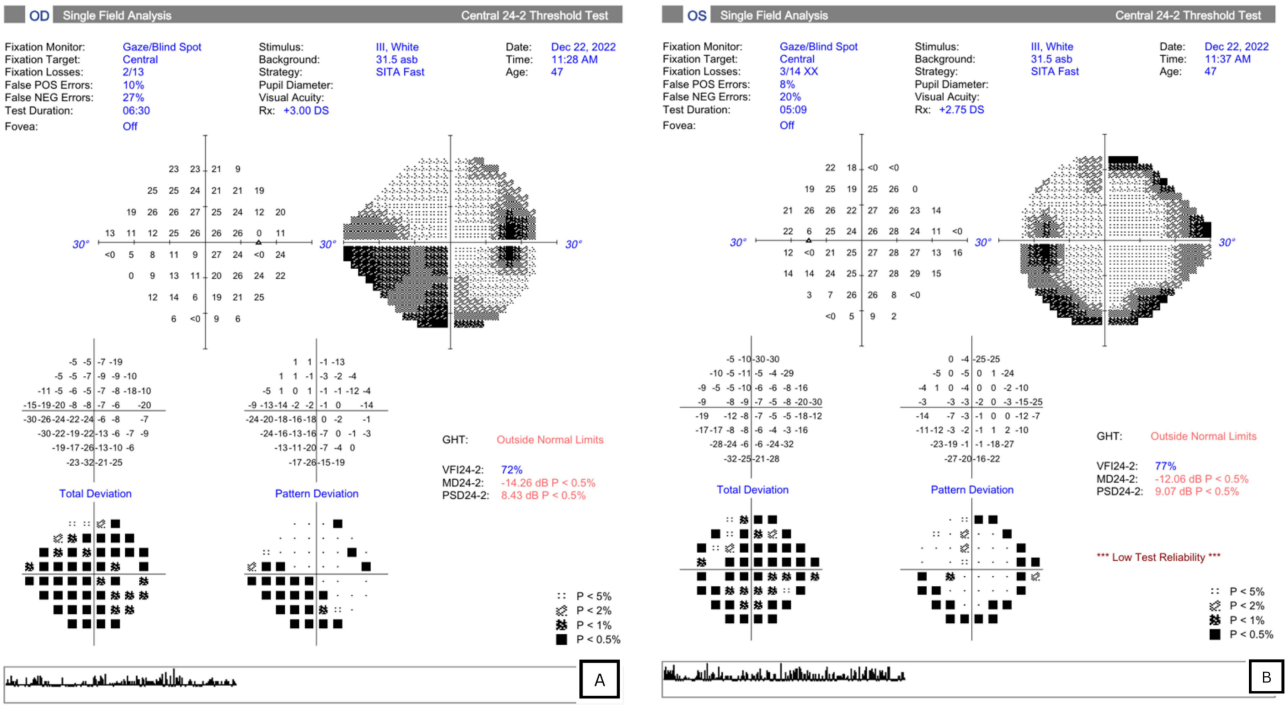

Figure 6 HFA 30–2 test in the right (**A**) and left (**B**) eye. Marked scotoma in the right eye with low test reliability of the LE.

edema, a shallow anterior chamber, and a moderate nuclear sclerotic cataract. Both eyes had a moderate nuclear sclerotic cataract. Examination of the posterior pole was challenging due to being obscured by the significant corneal edema.

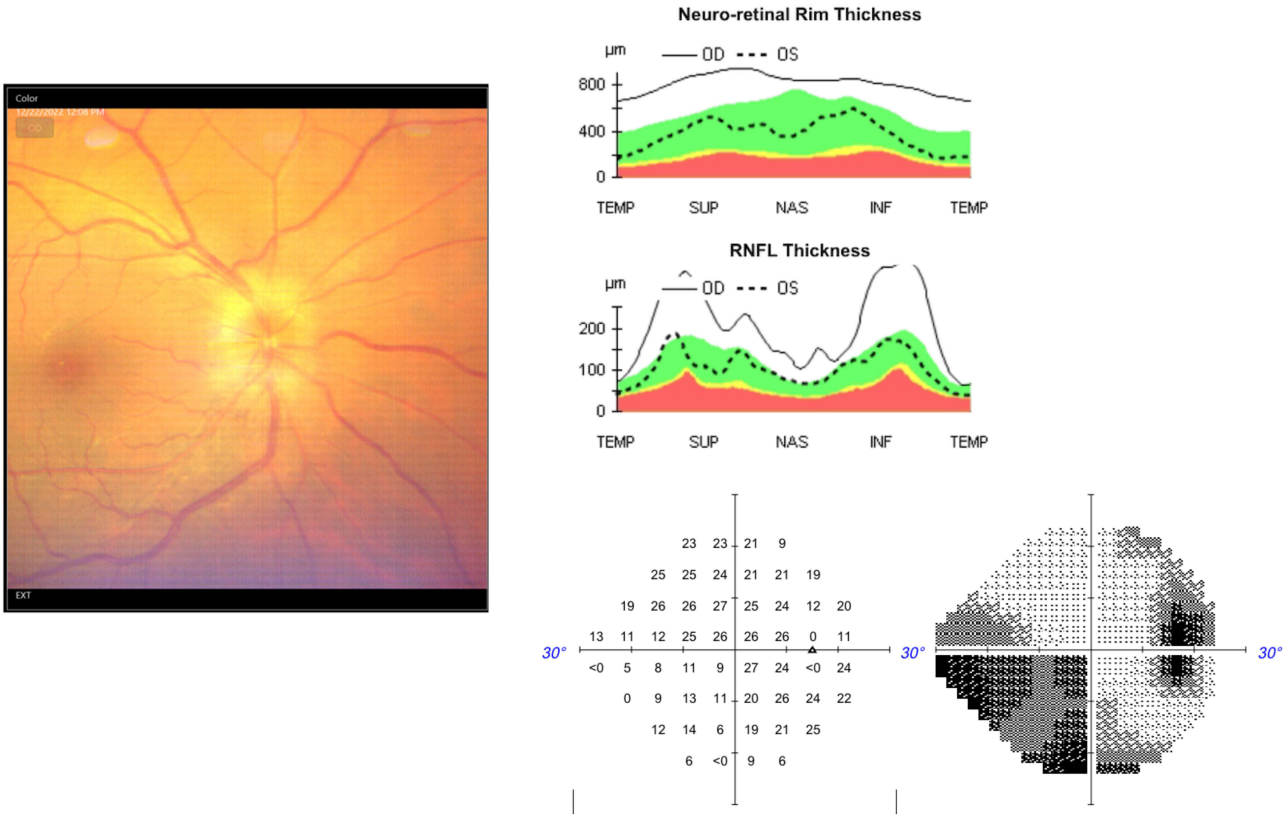

Figure 7 Case 1 - OCT ONH exhibiting diffuse optic disc edema, with a swollen optic nerve head diffusely, displaying increased thickness markers in the superior and inferior quadrants. This condition led to a significant scotoma in the Humphrey visual field analysis (HFA) of the right eye.

The patient was diagnosed with acute angle-closure glaucoma with concomitant non-arteritic anterior ischemic optic neuropathy (NAION) in the left eye, and a laser peripheral iridotomy (LPI) was performed in both eyes. The anterior chamber deepened after LPI with patent peripheral iridectomy. The patient received treatment with latanoprost/timolol, brinzolamide/brimonidine tartrate, prednisolone acetate, Carpine-2%, and oral acetazolamide.

Three days after starting the therapy, when the patient returned for a follow-up, the intraocular pressure (IOP) was measured at 9 mmHg in the right eye and 10 mmHg in the left eye. BCVA was improved to 1.0 in both eyes after treatment. Posterior pole evaluation revealed a crowded disc (CDR 0.1) in the right eye and segmental optic disc edema in the left eye. Further assessments were conducted, including optical coherence tomography (OCT) of the optic nerve head (ONH) (Figure 8A), ganglion (B), and visual field testing (Figure 9 and Figure 10). OCT ONH reveals edema in the left eye, indicative of swelling in the optic nerve. Concurrently, there is a noted crowded disc in the fellow eye, with a measured cup-to-disc ratio of 0.029. The ganglion OCT scan shows mild elevation in both eyes. HFA visual field testing reveals a superior arcuate field defect in the left eye. However, HFA testing was deemed unreliable (Figure 9A and B). A week after the initial diagnosis, repeat HFA testing showed improved reliability, revealing defects in both eyes (Figure 10A and B). Blood examinations showed increased of LDL and cholesterol levels, elevation of blood glucose, and increased of D-dimer levels.

Case 3

A 68-year-old female patient presented with complaints in her right eye, including sudden onset of pain, blurred vision, redness, and tearing that began 8 hours ago. These symptoms were not experienced before. The patient denied any history of hypertension, diabetes, or hypercholesterolemia. Visual acuity assessment revealed BCVA of 0.4 and 0.6 in the right and left eyes, respectively. Intraocular pressure (IOP) measurements were 60 mmHg in the right eye and 33 mmHg in the left eye.

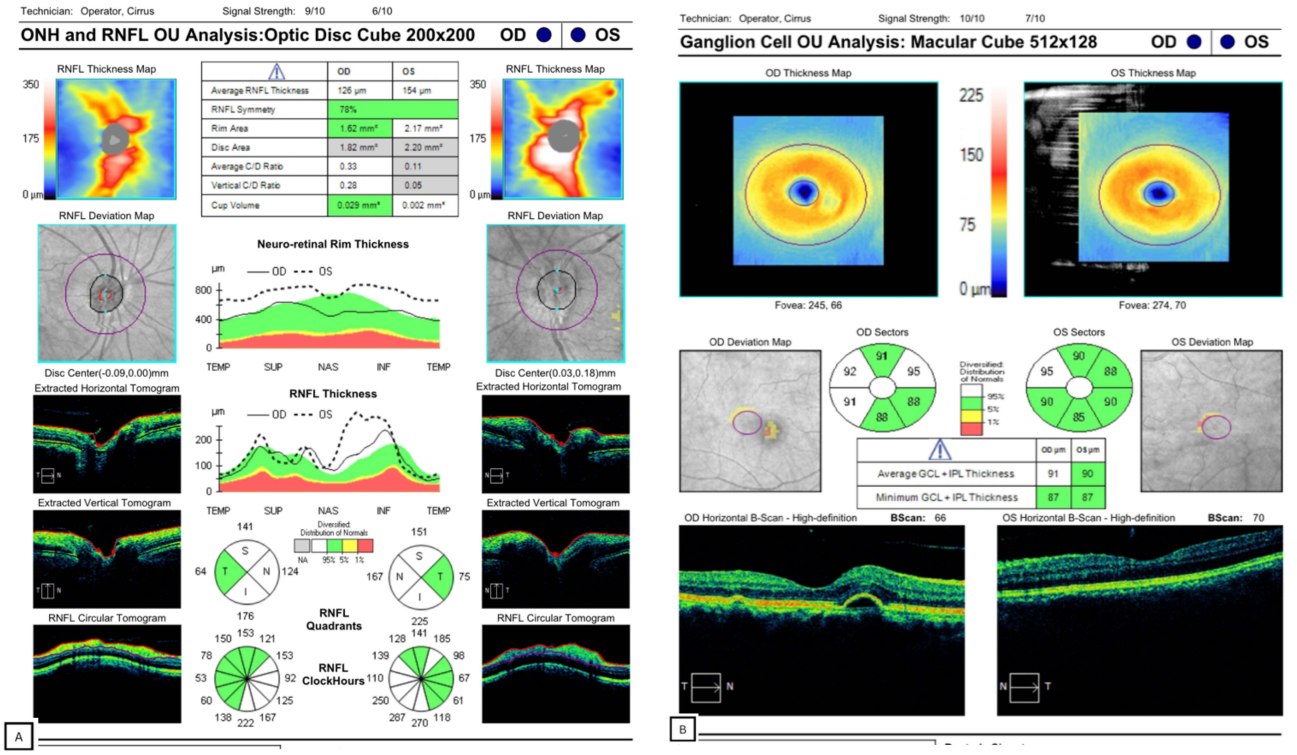

Figure 8 (**A**) OCT of the optic nerve head shows optic nerve edema in the left eye, with crowded disc (0.029) in the fellow eye. (**B**) Ganglion OCT shows no abnormality in both eyes.

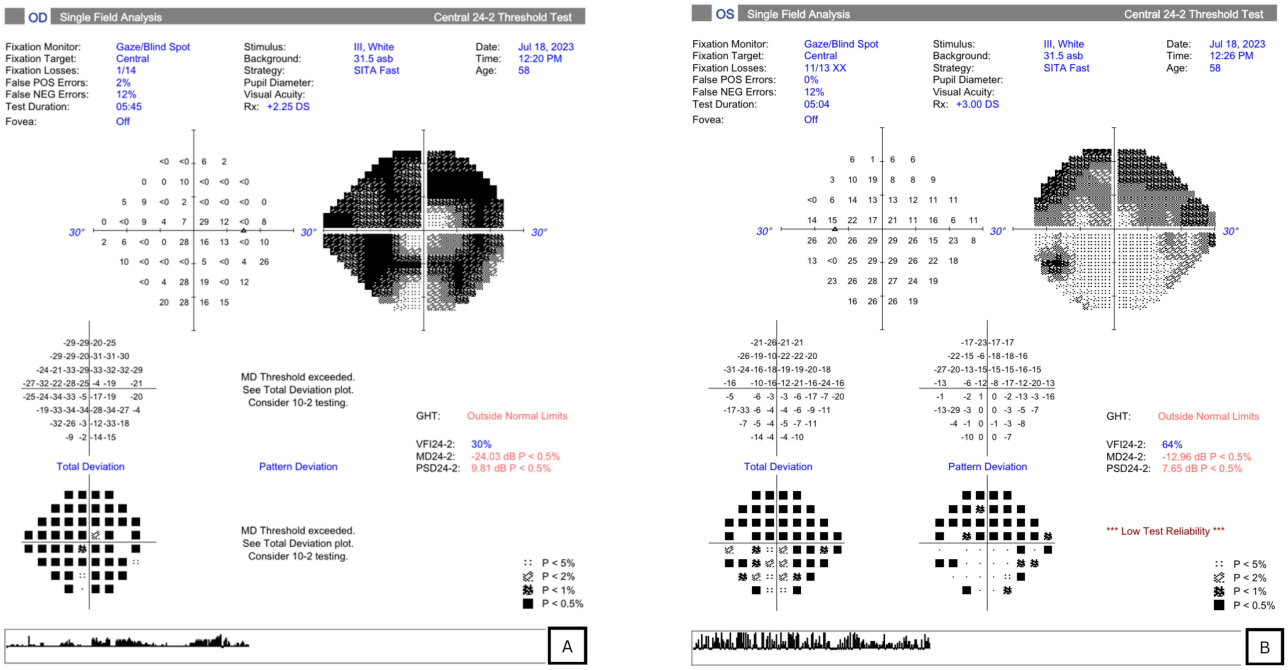

Figure 9 HFA visual field testing demonstrates superior arcuate field defect in the left eye (**A**). HVF testing in the right eye was not reliable (**B**).

The right eye exhibited moderately severe ciliary injection, corneal edema, a shallow anterior chamber with peripheral closure, a dilated pupil, and a moderate nuclear sclerotic cataract. On the other hand, the left eye was relatively quiet, with a shallow anterior segment (approximately 1/4 of corneal thickness peripherally), and a mild

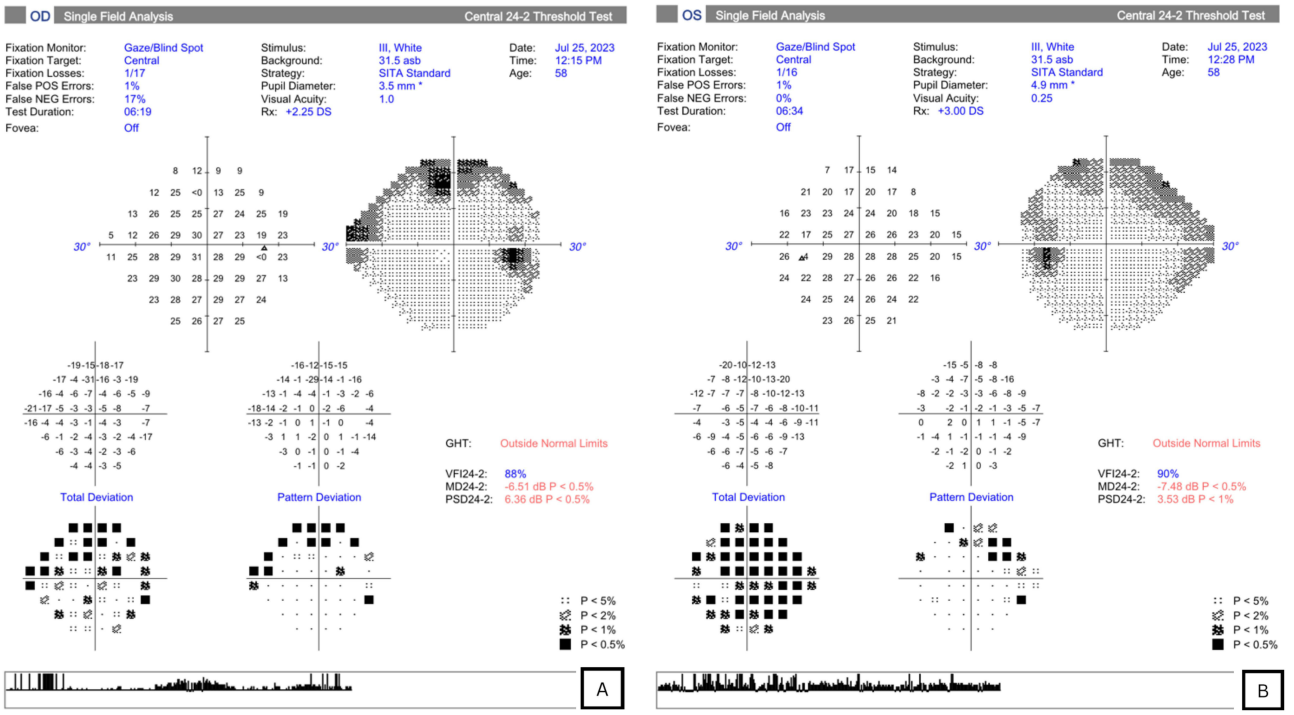

Figure 10 (**A, B**) HVF testing a week after initial diagnosis with better reliability with defect in both eyes.

nuclear sclerotic cataract. Due to corneal edema, the view of the posterior segment in the right eye was obscured and could not be examined. However, the left optic nerve head appeared crowded, with a cup-to-disc ratio of 0.1.

The patient received treatment for acute angle closure glaucoma in the right eye, which involved oral acetazolamide, latanoprost/timolol, and brinzolamide. After five days of treatment, the patient reported a marked improvement in pain; however, there was no significant improvement in vision. Best-corrected visual acuity (BCVA) was measured at 0.8 in the right eye and 1.0 in the left eye. Intraocular pressure (IOP) was recorded at 42mmHg in the right eye and 12mmHg in the left eye. The pupil was dilated, and marked corneal edema was observed. Due to the corneal edema, the posterior pole could not be evaluated.

To address the condition, a laser peripheral iridotomy (LPI) was performed, and the patient received treatment with brinzolamide/brimonidine, latanoprost/timolol, pilocarpine 2%, prednisolone acetate, and oral acetazolamide. One week after the LPI treatment, the IOP decreased to 9mmHg, and the anterior chamber deepened, with an improvement in corneal edema. However, it was noticed there was optic disc edema in the posterior pole of the right eye. The optic nerve head optical coherence tomography (ONH OCT) demonstrated diffuse swelling of the right optic nerve head, with retinal nerve fiber layer (RNFL) involvement in all quadrants (Figure 11A and B). Despite this finding, there were no visual field defect (Figure 12). Platelet aggregation tended to be hypoaggregative, and D-Dimer levels were elevated (690). Blood examinations indicated increased levels of total cholesterol and LDL. Brain and orbit magnetic resonance imaging (MRI) results were within normal limits, showing no compressive or infiltrative lesions. The patient was diagnosed with impending NAION secondary to AACG.

All enrolled patients were female, with angle-closure glaucoma demonstrating a threefold higher risk in the Asian population (Table 1).[9] In the onset of acute angle-closure glaucoma (AACG), intraocular pressure (IOP) was initially measured, and all values were above 55 mmHg. Crowded discs in the fellow eyes were observed in all patients, which is a common risk factor for NAION.[10] Patients diagnosed with concomitant non-arteritic anterior ischemic optic neuropathy (NAION) secondary to acute angle attack had risk factors, including elevated LDL and cholesterol levels, an increase in blood glucose level, and an elevation of D-dimer. One patient diagnosed with impending NAION secondary to AACG presented with no systemic risk factors. In the third case, without any systemic findings, other risk factors needed to be

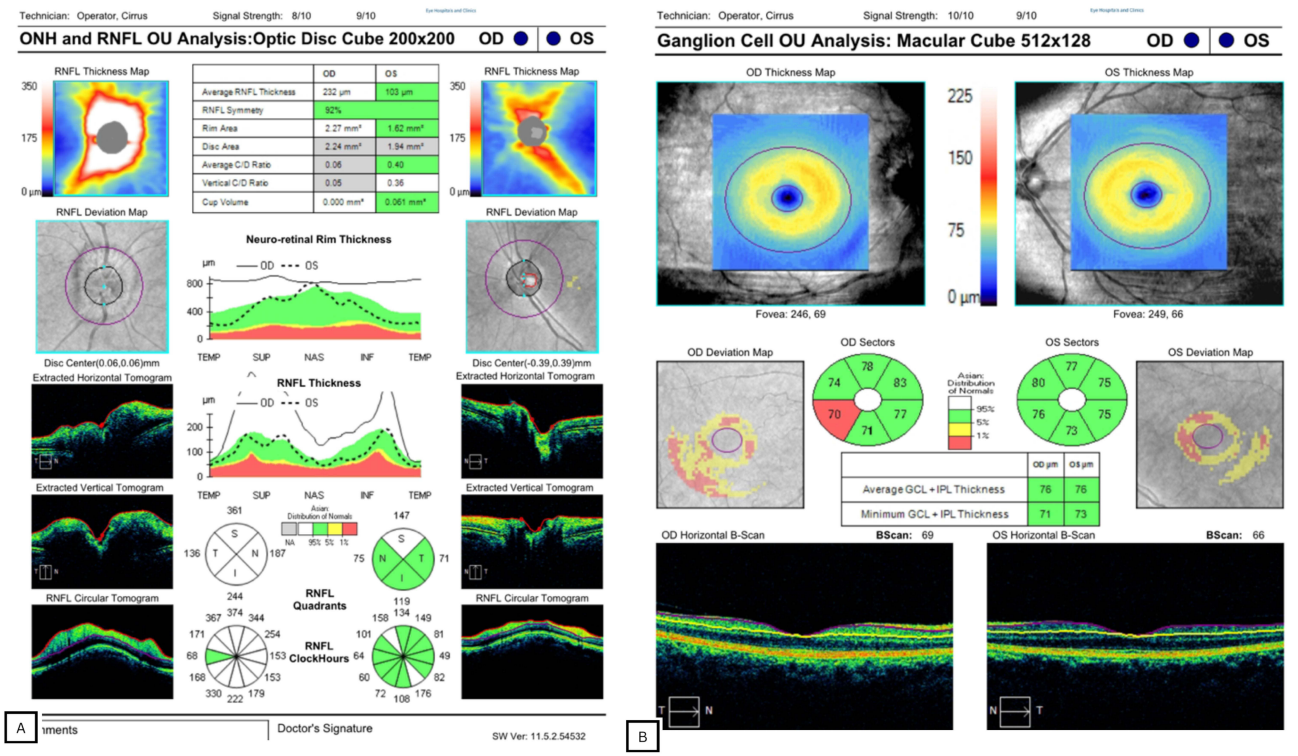

Figure 11 (**A**) ONH OCT with marked disc edema 360 in all quadrants of the right eye compared to the left eye (**B**) Ganglion OCT showed no significant defect in both eyes.

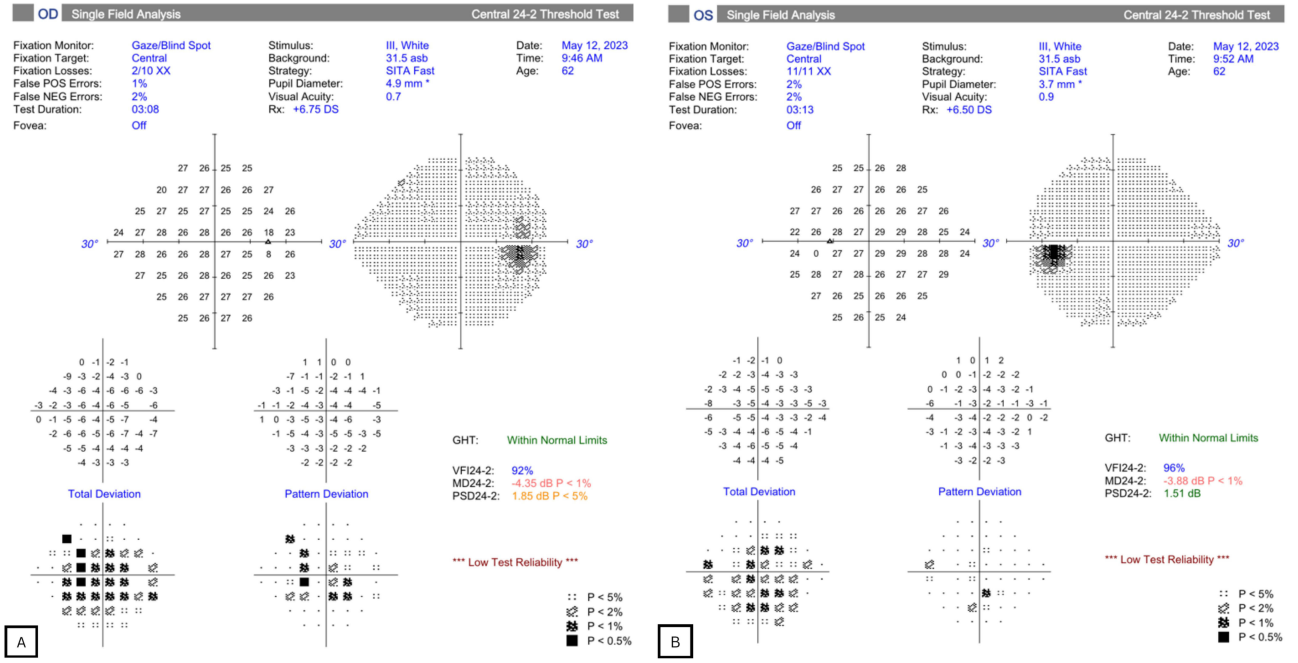

Figure 12 (**A**, **B**) Visual field test results obtained using the Humphrey visual field analyzer (HFA), showing no significant defects in the right eye.

Table 1 Summary of the Cases

Case	Age	Gender	Eye	IOP (mmHg)	VF defect	Systemic findings
1	48	F	OD	62	Inferior	Elevated LDL and cholesterol
2	58	F	OS	63	Superior arcuate	Elevated LDL, total cholesterol, elevated D-dimer, increased blood glucose
3	68	F	OD	60	No defect	-

examined. Other markers found to be possibly correlated with NAION include cardiovascular disease, stenosis, sleep apnea, hyperhomocysteinemia, and factor V Leiden heterozygous.[3]

Discussion

NAION is marked by the sudden loss of vision in one eye due to a disruption in the blood supply to the optic nerve.[11] Unlike acute angle closure, which primarily affects the drainage angle, NAION involves damage to the optic nerve itself.[12] The precise mechanism underlying NAION remains unclear. Nevertheless, it is hypothesized that the condition arises from vascular insufficiency, resulting from disrupted autoregulation of small vessels in the posterior ciliary circulation. This disturbance ultimately results in ischemia of the optic nerve head.[8,10]

The hypothesis was postulated that the elevated intraocular pressure observed in glaucoma might be attributed to the similarity in protein expression within the ocular extracellular matrix of the trabecular meshwork and the lamina cribosa. However, it's essential to recognize that abnormal collagen metabolism could be just one contributing factor to the damage seen in these tissues. Both the trabecular meshwork and lamina cribosa share inherent functional and biochemical similarities. These tissues play dual roles, responsible for and dependent upon maintaining a network of collagenous beams that provide structural strength, flexibility, and compliance. Beyond collagens, various molecules are crucial for the functionality of these beams. Additionally, the matrices external to these beams have identical components in both tissues. Both the trabecular meshwork and lamina cribrosa make insertions into the adjacent sclera, making them susceptible to biochemical or biomechanical influences from that tissue.[13–16] This biochemical similarity between human trabecular meshwork and lamina cribrosa cells directly implicates trauma to increase intraocular pressure, potentially accounting for concurrent cellular dysfunction in these tissues and contributing to the disease's etiology and progression. The abnormal metabolism and protein expression in the trabecular meshwork and lamina cribrosa caused by trauma may result from the elevation of intraocular pressure.[17,18]

Our hypothesis suggests that trauma induced by a sudden increase in intraocular pressure during an acute glaucoma attack results in similar protein expression in the lamina cribrosa. The lamina cribrosa is implicated in various neurodegenerative diseases, with proposed contributions from biomechanical and vascular factors, including glaucoma and non-arteritic anterior ischemic optic neuropathy (NAION). In the case of NAION, the primary lesion is believed to be situated at or near the level of the lamina cribrosa in the anterior optic nerve.[19] The impact of increased intraocular pressure in glaucoma extends to extracellular matrix remodeling in the trabecular meshwork, resulting in heightened resistance to outflow. This pressure also induces remodeling of the lamina cribrosa, the collagenous tissue at the optic nerve head, ultimately leading to optic neuropathy.[20] Alterations in the lamina cribrosa, whether due to compression or ischemia, are associated with occurrence of NAION. Matricellular proteins, a subset of non-collagenous extracellular matrix proteins, are implicated in the pathogenesis of glaucoma, including NAION. These proteins play a role in regulating cellular interactions, tissue remodeling, and inflammatory processes, potentially influencing the onset and progression of NAION.[20–23]

In response to the elevation of intraocular pressure, the optic nerve head is able to preserve a stable blood flow within a specific IOP range. However, this defense is absent or diminishes as IOP reaches 45 or 55 mm Hg, resulting in decreased blood flow, which leads to ischemia.[24] Non-arteritic anterior ischemic optic neuropathy (NAION) is thought to be caused by a lack of blood flow to the optic nerve head (ONH). A significant increase in intraocular pressure (IOP) can

reduce the blood flow to the ONH by compressing the blood vessels in the prelaminar region therefore lead to NAION. The choroidal blood supply to the ONH and peripapillary choroid is most susceptible to IOP elevation.[22,23]

The relationship between acute primary angle-closure (APAC) and non-arteritic anterior ischemic optic neuropathy (NAION) remains uncertain, and when considering this hypothesis, no definitive conclusions can be drawn regarding whether APAC is causally linked to NAION or results from it.[25] The association between these conditions is considered to be a potential link, and additional research is necessary to gain a comprehensive understanding of their interrelationship. In NAION cases, a crowded optic disc is frequently noted due to reduced perfusion or ischemia of the optic nerve head within a small disc morphology and is aggravated by increased intraocular pressure during a glaucoma attack. Regarding the presumed mechanism leading to NAION, it is believed to result from decreased perfusion to the optic disc due to an increase in intraocular pressure (IOP).[26] An elevation in intraocular pressure is believed to potentially hinder blood flow to the optic nerve head, leading to ischemia. This underscores the significance of controlling pressure in all cases to prevent the occurrence of non-arteritic anterior ischemic optic neuropathy (NAION).[27] In glaucoma, increased intraocular pressure (IOP) can impede blood flow, reducing the energy supply and potentially affecting axonal transport. Axoplasmic stasis, characterized by slowed or stagnant axoplasmic flow within optic nerve fibers, can ensue, leading to nerve fiber and optic disc swelling. This swelling may compress the delicate, low-pressure venules in the superficial nerve fiber layer and prelaminar region, resulting in venous stasis and fluid leakage. Consequently, extracellular fluid accumulates. This pathomechanism contributes to the development of both non-arteritic anterior ischemic optic neuropathy (NAION) and glaucoma.[28] Another hypothesis is that the NAION developed first and triggered an acute angle closure attack in a patient with a susceptible occludable anterior chamber angle. An increase in choroidal thickness has been previously identified in patients with NAION and it could be the factor required to modify the anatomy of the ciliary body pushing it forward and occluding a previously predisposed narrow angle.[29,30]

According to our hypothesis, what distinguishes patients in this case series, where an increase in intraocular pressure occurs during a glaucoma attack and may lead to NAION, is the risk of a crowded disc as an anatomical risk factor. Therefore, patients with risk factors for glaucoma attacks should also have their disc configuration examined to prevent the occurrence of NAION or take preventive measures against NAION attacks in the fellow eye.[31,32] This can be achieved through the evaluation of systemic factors. The likelihood of NAION recurrence in the same eye is relatively low, estimated at 3–5%. However, the recurrence rate in the contralateral eye is high, ranging from 15–20% in 5 years.[33,34] Consequently, patients, particularly those highlighted in this case, should undergo further assessment and be made aware of this condition to improve disease outcomes. This awareness is crucial not only for preventing visual loss resulting from acute glaucoma attacks but also for mitigating the risk of recurrent NAION in the same eye and the fellow eye.

This series of cases highlights the significance of recognizing the crucial link between acute optic nerve injury, optic neuropathy, and abrupt elevations in intraocular pressure (IOP) in patients with crowded disc anatomical risk factors. It underscores the imperative for prompt and proactive interventions to prevent the risk of irreversible damage. The occurrence of non-arteritic anterior ischemic optic neuropathy (NAION) as a result of acute primary angle-closure (APAC) is an infrequent but potentially vision-compromising clinical phenomenon.

Ethics Approval and Informed Consent

The case report study underwent review and approval from the internal review ethics board at JEC Eye Hospitals and Clinics. All three patients provided written informed consent for their case details to be published.

Disclosure

The authors report no conflicts of interest in this work.

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