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Optic nerve edema or swelling in inflammatory and ischemic neuropathy: a review

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This paper reviews the current insights into, and prospects for better understanding of, the pathogenesis of optic nerve edema or swelling in the presence of inflammatory or ischemic optic neuropathy. Forty-six Ukrainian and foreign publications on the subject were reviewed and considered. There are several theories of optic nerve damage due to swelling (edema); these include biomechanical theories (features of structural components, a change in the optic nerve architecture, and stretching of the Bruch membrane) and an ischemic theory (abnormal perfusion and axonal transport stasis). Of importance are also abnormal vascular permeability and exudation of plasma and blood cells, which results in accumulation of fluid, inflammatory mediators and metabolic products between peripapillary retinal layers, impeding the outflow and metabolism in the posterior segment of the eye. Current neuroimaging techniques (optical coherence tomography (OCT) and OCT angiography) facilitate improved understanding of structural changes in the optic nerve head. Therefore, studies on optic disc architecture, fluid circulation in the posterior segment, and interaction of optic nerve head components in optic nerve edema or swelling will facilitate (a) improved understanding of the pathogenesis and (b) the differential diagnosis of acute optic neuropathies, and, consequently, will enable treatment for inflammatory and ischemic optic nerve lesions.

Keywords:

optic nerve, acute optic neuropathy, optic neuritis, ischemic neuropathy, OCT

Introduction

Optic nerve edema or swelling may develop in diseases of different etiology. In optic nerve inflammation (or papillitis), optic edema develops within hours after demyelination injury or a viral or bacterial infection, and progresses rapidly [1]. Optic nerve swelling is considered a component of the pathogenesis of, and a sign of the activation of secondary damage pathways in, ischemic optic neuropathy [2].

The mechanisms of the development of optic atrophy secondary to papilledema are being extensively studied. Cell neurotoxicity, activation of autoimmune reactions and impaired neurotransmitter circulation due to ganglion cell death induced by the primary factor are some of the potential causes being considered. In the presence of optic edema, the area of damage increases due to nerve compression and toxicity of own dead cells [3].

Edema or swelling affects the optic nerve architecture. There is a need to clarify the way in which the change from edema (or swelling) to atrophy of optic disc components (and vice versa if secondary lesions develop) occurs to decide whether the pathological process will stabilize or progress [4].

Current diagnostic techniques provide an increasing amount of data on the pathogenesis of optic nerve edema or swelling and thus contribute to the development of advanced treatment modalities.

The purpose of this paper was to review the current insights into, and prospects for better understanding of, the pathogenesis of optic nerve edema or swelling in the presence of inflammatory or ischemic optic neuropathy.

Forty-four Ukrainian and foreign publications on the subject were reviewed and considered.

Terminologies used for optic disc edema

Many terms have been used in the literature for optic disc edema. Papilledema is a term generally reserved (at least in the English language use of the term) by neuro-ophthalmologists for optic disc edema due to increased intracranial pressure [5]. The term ‘pseudotumor cerebri’, in the past commonly used as a synonym of idiopathic intracranial hypertension, is now used as an umbrella term that describes the chronic elevation of intracranial pressure. Pseudotumor cerebri most frequently presents with bilateral optic disc swelling; however, case reports and series have reported patients with either symmetrical or truly unilateral swelling [6].

Optic nerve head elevation may be due to a variety of etiologies, including benign cases such as anatomic variants or high hyperopic refractive error [7]. However, optic nerve head elevation may also be a sign of vision- or life-threatening conditions such as elevated intracranial pressure, idiopathic intracranial hypertension of intracranial

tumors [7]. Unlike papilledema, pseudopapilledema is a group of optic disc anomalies whose common element is elevation of the optic disc without true swelling of the axonal fibers. In addition, reduced visual acuity typically is not observed in pseudopapilledema [8].

Common causes of optic nerve head elevation because of optic disc edema include elevated intracranial pressure (papilledema), optic neuritis (papillitis), diabetic or hypertensive papillitis [9], anterior ischemic optic neuropathy (AION), neuroretinitis, uveitis, compression, or infiltration.

Sadun and Wang (2011) proposed their classification of the conditions resulting in optic nerve edema or swelling [10].

Chiang and colleagues [11] reported on the usefulness of multimoldal imaging (including B-scan ultrasonography and optical coherence tomography) for differentiating pseudopapilloedema and true swelling of the optic nerve head.

Features of inflammatory swelling of the optic nerve

Sudden vision loss with optic nerve swelling in young individuals is most typical for optic neuritis [12].

It is due to optic nerve swelling that an atypical course of optic neuritis [13] should be differentiated from ischemic neuropathy [14, 15].

Unilateral unspecified or bilateral optic neuritis (9C40 as per ICD-11) is accompanied by optic nerve swelling. Visual loss is typical for demyelinating optic neuritis [16].

In some cases, papillitis and optic nerve swelling may be caused by paranasal sinusitis [17]. Under such circumstances, optic neuropathy develops due to optic compression, which results in loss of optic nerve fibers [18, 19].

In pediatric optic neuritis, optic nerve swelling is typically more apparent than in adult optic neuritis, and is commonly bilateral [20, 21].

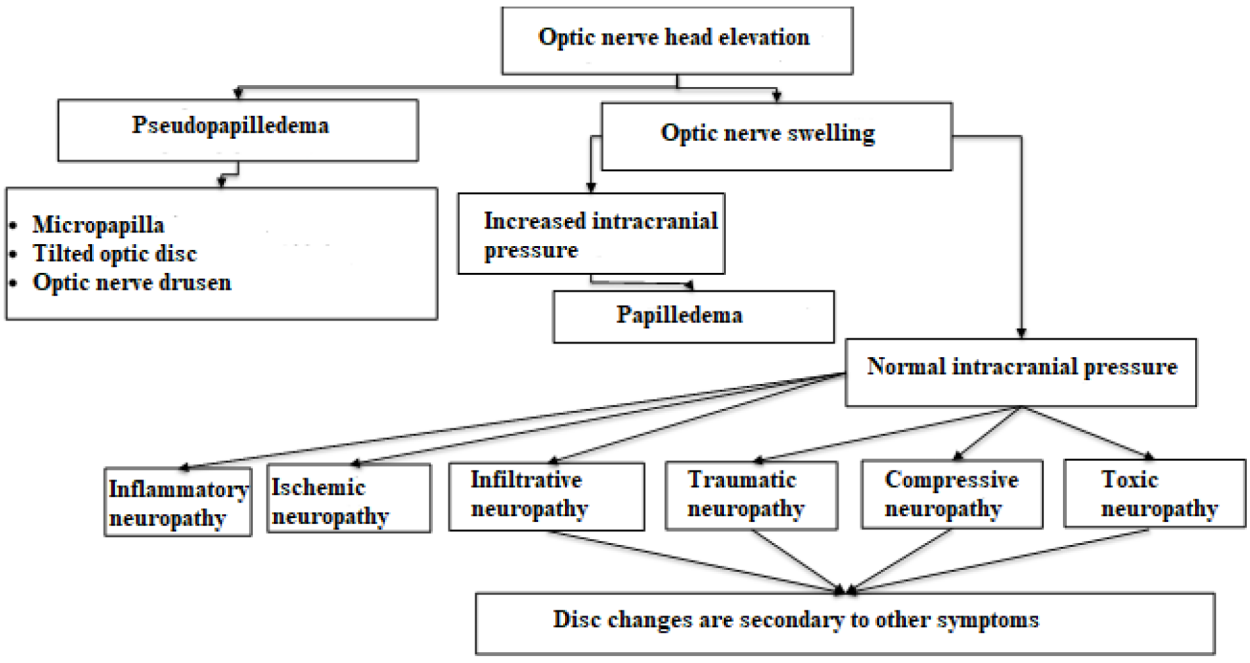
Optic neuritis can result in optic atrophy [22]. Peripapillary region is most commonly affected, with crescent-shaped neuroretinal rim thinning developing similar to that in glaucoma or degenerative myopia [23].

De Carlo and colleagues (2015) [24] demonstrated that, in eyes with birdshot chorioretinopathy (BSCR) complicated by optic edema, a crescent-shaped light area may develop in the peripapillary region which separates the temporal border of the optic disc. Blood flow and fluid perfusion in this region were affected [24]. In the eye of a patient with BSCR, the prelaminar optic disc showed a lymphocytic focus, with inflammatory cell accumulation resulting in damage to the structural components of the optic disc [25].

Optic disc swelling extending to the retinal pigment epithelium (RPE)/Bruch's complex may also have a negative effect. Khodeiry and colleagues [26] hypothesize that circumferential peripapillary halos (versus crescentic peripapillary atrophy) is the result of swelling of the optic disc secondary to BSCT papillitis secondary to stretching, thinning and tearing of the retinal layers attached to and surrounding the optic disc border.

Features of optic nerve swelling in ischemic optic neuropathy

Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common acute optic neuropathy



Scheme 1. Classification of optic disc edema or swelling

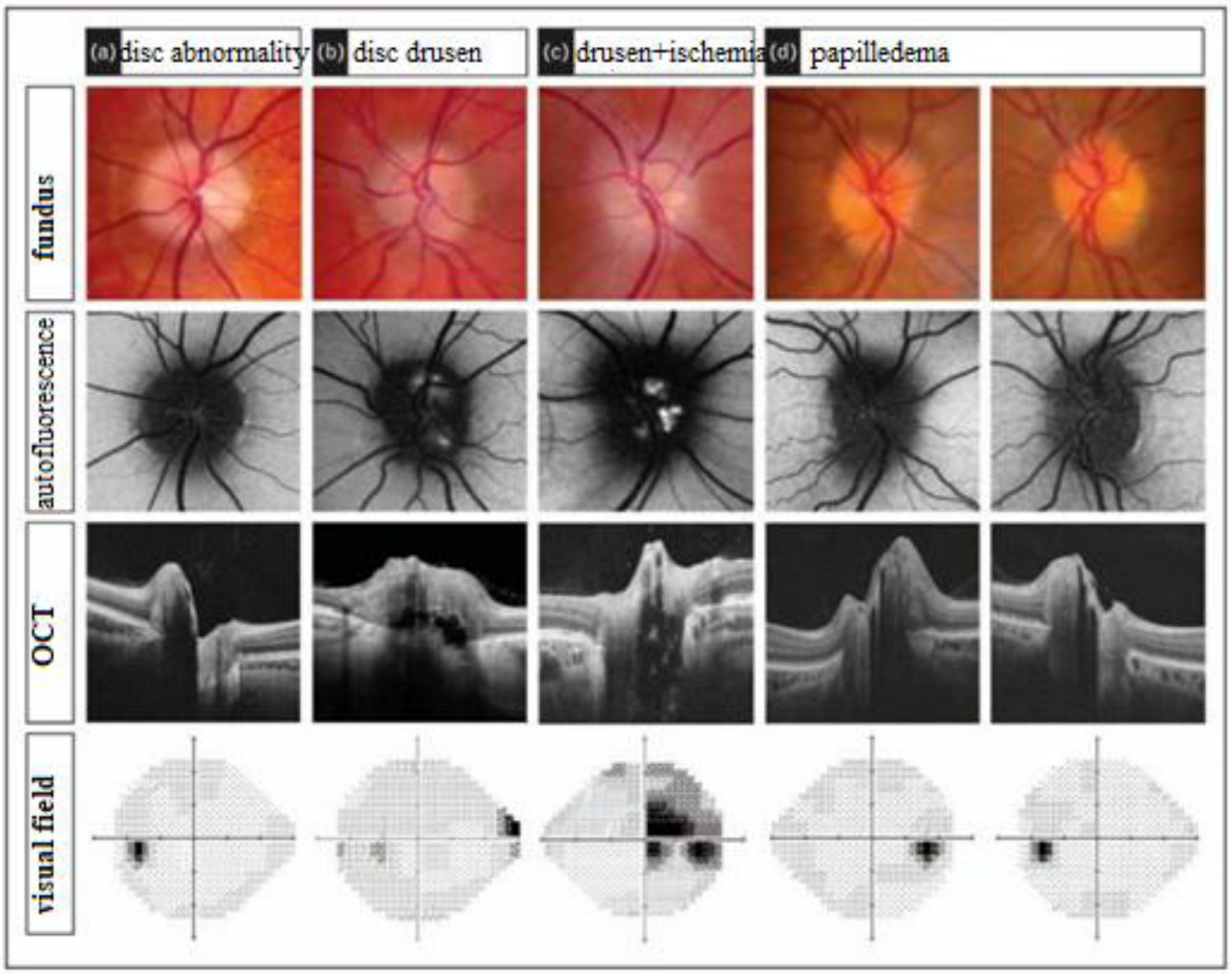


Figure 1. Disc configuration changes in edema or swelling of various etiologies and their relationship with visual fields

in people aged 50 and older. NAION is characterized by optic disc edema and sudden, painless visual loss [27]. The condition is caused by infarction of the laminar or retrolaminar portion of the optic disc due to the impaired blood supply from the central retinal artery or short posterior ciliary arteries [28].

The mechanisms of progression of ischemic optic neuropathy have been poorly studied [29, 30]. It is likely that compression of optic disc capillaries by swollen axons increases the ischemic lesion and promotes axonal swelling, thus expanding the infarction region to other optic disc locations [31].

Progressive NAION showed development of the disc swelling from the superior to the inferior portion of optic disc. During progression, eyes with progressive NAION showed a significant increase in the circumpapillary retinal nerve layer thickness (cpRNFLT) in the inferior quadrants; furthermore, there was significant increase in cpRNFLT in the nasal sector before visual loss developed after the initial visit. In addition, a study by Hashimoto and colleagues [32] demonstrated thickened RNFL in the superior portion during the first episode, and the spread to the inferior portion during the second episode in all cases. In contrast, eyes with diffuse optic swelling during the first episode of NAION seldom progressed.

The Zinn-Haller circle is an anastomotic circle between the lateral and medial short posterior ciliary arteries, which perfuses the optic head. However, some cases have incomplete anastomoses or the Zinn-Haller ring is supplied only by the lateral or medial short posterior ciliary artery, and those eyes are vulnerable to anterior optic nerve ischemia. Hypoperfusion from the lateral short posterior ciliary artery may occur in the superior portion of the optic disc, resulting in the superior disc swelling, followed by hypoperfusion from the medial short posterior ciliary artery [33].

OCT evidence of swelling-induced changes in the optic nerve head

Although the forces acting on the nerve head in papilledema differ from those in glaucoma, the application of biomechanical principles may provide insights about the clinical effects of intracranial pressure on the optic nerve head. It is believed that optic disc swelling (papilledema) is a consequence of axonal distension of the prelaminar and

peripapillary nerve fibers. Vascular congestion, leakage, and ischemia follow the acute axoplasmic flow stasis and are associated with interstitial edema, which exerts pressure on and causes the deformation of the optic disc. Axonal, glial and vascular dysfunction results in lesion progression [34].

Ischemia and increased fluid accumulation around the disc are a factor considered for the development of lesions in optic disc swelling. Studies have confirmed that prelaminar axoplasmic flow stasis results in increased vascular permeability and extravasation of axoplasm into the perineural space of the optic nerve [34, 35]. The limited space of optic nerve head is another factor contributing to the development of lesions due to hypoperfusion and axoplasmic flow stasis [36].

The OCT allows assessing swelling-induced changes in the peripapillary retinal nerve fiber layer (RNFL) thickness [37]. It is likely that RNFL thickness depends on the cause of edema or swelling [38]. This principle underlies the differential diagnosis (Fig. 1) of causes of edema according to disc configuration [39, 40].

Because of the different pathophysiology of disc edema caused by retinal vein obstruction compared with inflammatory optic neuropathies, it is believed that, in inflammatory optic neuropathies, edema is found predominantly in the RNFL and the ganglion cell layers [41]. It is believed that, in retinal vein occlusion, edema predominantly affects all retinal layers [42].

Peripapillary hemorrhages and fluid accumulation [43, 44] due to peripapillary vein occlusion change the reflection of light by the RNFL. In such a case, OCT sector scanning will yield white sectors. Such findings are considered as increased RNFL thickness or an obstacle for the reflected light passing through the RNFL.

The recent advent of OCT angiography (OCTA) has made it possible to perform a more detailed assessment of changes in optic disc components due to the impact of edema. In ischemic optic neuropathy and other acute conditions, peripapillary hyper-reflective ovoid mass-like structures (PHOMS) often lie external to and surrounding large parts of the disc, which confirms the hypothesis of compression of optic nerve fibers in the prelaminary optic nerve head [45].

Fraser and colleagues (2021) [45] believe that nerve fiber displacement over Bruch membrane opening can change disc configuration and axonal transport capacity [45], with this displacement being a likely cause of a non-uniform pattern of expansion of edema among peripapillary retinal layers and impaired relationships among neural cells. In addition, Fraser and colleagues [45] reported on the appearance of PHOMS in a patient with isolated demyelinating optic neuritis.

Conclusion

Forty-six recent publications on optic nerve edema or swelling from inflammatory or ischemic optic neuropathy were reviewed. It was found that optic nerve edema or swelling is characterized by special features, but it is difficult to identify the symptoms for making the differential diagnosis between the two conditions. There are several theories of optic nerve damage due to swelling (edema); these include biomechanical theories (features of structural components, a change in the optic nerve architecture, and stretching of the Bruch membrane) and an ischemic theory (abnormal perfusion, axonal transport stasis, and venous insufficiency). Of importance are also abnormal vascular permeability and exudation of plasma and blood cells, which results in accumulation of fluid, inflammatory mediators and metabolic products between peripapillary retinal layers, impeding the outflow and metabolism in the posterior segment of the eye [46]. Current neuroimaging techniques (OCT and OCTA) facilitate improved understanding of structural changes in the optic nerve head. They are still not widely used in acute neuropathies, because OCT and OCTA parameters have been not introduced in classifications and diagnostic standards. Therefore, studies on optic disc architecture, fluid circulation in the posterior segment, and interaction of optic nerve head components in optic nerve edema or swelling will facilitate (a) improved understanding of the pathogenesis and (b) the differential diagnosis of acute optic neuropathies, and, consequently, will enable treatment for inflammatory and ischemic optic nerve lesions.

References

1. Chan JW. Optic neuritis in multiple sclerosis. Ocul Immunol Inflamm. 2002;10:161-86.
2. Berry S, Lin WV, Sadaka A, Lee AG. Nonarteritic anterior ischemic optic neuropathy: cause, effect, and management. Eye Brain. 2017 Sep 27;9:23-28.
3. Rodríguez Villanueva J, Martín Esteban J, Rodríguez Villanueva LJ. Retinal Cell Protection in Ocular Excitotoxicity Diseases. Possible Alternatives Offered by Microparticulate Drug Delivery Systems and Future Prospects. Pharmaceutics. 2020 Jan 24;12(2):94.
4. Margolin E. The swollen optic nerve: an approach to diagnosis and management. Pract Neurol. 2019 Aug;19(4):302-309.
5. Lee A, Rigi M, Al marzouqi S, Morgan M. Papilledema: epidemiology, etiology, and clinical management 2015;7-47.
6. Lawlor M, Zhang MG, Virgo J, Plant GT. Asymmetrical Intraocular Pressures and Asymmetrical Papilloedema in Pseudotumor Cerebri Syndrome. Neuroophthalmology. 2016 Oct 5;40(6):292-296.
7. Cavuoto KM, Markatia Z, Patel A, Osigian CJ. Trends and Clinical Characteristics of Pediatric Patients Presenting to an Ophthalmology Emergency Department with an Initial Diagnosis of Optic Nerve Head Elevation. Clin Ophthalmol. 2022 May 18;16:1525-1528.
8. Rebolleda G, Kawasaki A, de Juan V, Oblanca N, Muñoz-Negrete FJ. Optical Coherence Tomography to Differentiate Papilledema from Pseudopapilledema. Curr Neurol Neurosci Rep. 2017 Aug 17;17(10):74.
9. Hayreh SS. Pathogenesis of optic disc edema in raised intracranial pressure. Prog Retin Eye Res 2016; 50:108–144.
10. Sadun AA, Wang MY. Abnormalities of the optic disc. Handb Clin Neurol 2011; 102: 117–157.
11. Chiang J, Wong E, Whatham A, Hennessy M, Kalloniatis M, Zangerl B. The usefulness of multimodal imaging for differentiating pseudopapilloedema and true swelling of the

optic nerve head: a review and case series. Clin Exp Optom. 2015 Jan;98(1):12-24.
12. Fernandes DB, Ramos Rde I, Falcochio C, Apostolos-Pereira S, Callegaro D, Monteiro ML. Comparison of visual acuity and automated perimetry findings in patients with neuromyelitis optica or multiple sclerosis after single or multiple attacks of optic neuritis. J Neuroophthalmol. 2012;32(2):102–106.
13. Moyseyenko NM. Optic Neuritis or Inflammatory Optic Neuropathy: a review. J.ophthalmol.(Ukraine).2022;6:44-49.
14. Toosy AT, Mason DF, Miller DH. Optic neuritis. Lancet Neurol. 2014;13(1):83–99.
15. Monteiro MLR, Hokazono K, Cunha LP, Biccas Neto L. Acute visual loss and optic disc edema followed by optic atrophy in two cases with deeply buried optic disc drusen: a mimicker of atypical optic neuritis. BMC Ophthalmol. 2018 Oct 26;18(1):278.
16. Kale N. Optic neuritis as an early sign of multiple sclerosis. Eye Brain. 2016 Oct 26;8:195-202.
17. Nataliya Moyseyenko. The Effect of Secondary Neuritis on the Optic Nerve in Patients with Chronic Rhinosinusitis, 16 November 2023, PREPRINT (Version 1) available at Research Square.
18. Moyseyenko, N. (2023). Secondary sinusogenic neuritis and optic nerve atrophy. ScienceRise: Medical Science, 2(53), 16–20.
19. Del Noce C, Marchi F, Sollini G, Iester M. Swollen Optic Disc and Sinusitis. Case Rep Ophthalmol. 2017 Aug 3;8(2):421-424.
20. Suparmaniam S, Wan Hitam WH, Thilagaraj S. Bilateral Parainfectious Optic Neuritis in Young Patient. Cureus. 2022 Sep 16;14(9):e29220.
21. Birgit Lorenz, Michael C. Brodsky. Pediatric Ophthalmology, Neuro-Ophthalmology, Genetics. Strabismus - New Concepts in Pathophysiology, Diagnosis, and Treatment. Springer-Verlag Berlin Heidelberg 2010. 237 p.
22. Rath EZ, Rehany U, Linn S, Rumelt S. Correlation between optic disc atrophy and aetiology: anterior ischaemic optic neuropathy vs optic neuritis. Eye (Lond). 2003 Nov;17(9):1019-24.
23. See JL, Nicolela MT, Chauhan BC. Rates of neuroretinal rim and peripapillary atrophy area change: a comparative study of glaucoma patients and normal controls. Ophthalmology. 2009;116(5):840–847.
24. de Carlo TE, Bonini Filho MA, Adhi M, Duker JS. Retinal and choroidal vasculature in birdshot chorioretinopathy analyzed using spectral domain optical coherence tomography angiography. Retina. 2015;35 (11):2392–2399.
25. Gaudio P, Kaye D, Crawford JB. Histopathology of birdshot retinochoroidopathy. Br J Ophthalmol. 2002;86(12):1439–1441.
26. Khodeiry MM, Liu X, Sayed MS, Goldhardt R, Gregori G, Albini TA, Lee RK. Peripapillary Halo in Inflammatory Papillitis of Birdshot Chorioretinopathy. Clin Ophthalmol. 2021 Jun 3;15:2327-2333.
27. Fontal MR, Kerrison JB, Garcia R, Oria V. Ischemic optic neuropathy. Semin Neurol. 2007 Jul;27(3):221-32.
28. Kerr NM, Chew SS, Danesh-Meyer HV. Non-arteritic anterior ischaemic optic neuropathy: a review and update. J Clin Neurosci. 2009 Aug;16(8):994-1000.
29. Chen T, Ma J, Zhong Y. [Research advances in the risk factors of nonarteritic anterior ischemic optic neuropathy]. Zhonghua Yan Ke Za Zhi. 2013 Nov;49(11):1049-51.
30. Martin-Gutierrez MP, Petzold A, Saihan Z. NAION or not NAION? A literature review of pathogenesis and differential diagnosis of anterior ischaemic optic neuropathies. Eye (Lond). 2024 Feb;38(3):418-425.
31. Hayreh SS, Zimmerman MB. Incipient nonarteritic anterior ischemic optic neuropathy. Ophthalmology. 2007;114(9):1763–1772.
32. Hashimoto H, Hata M, Kashii S, Oishi A, Suda K, Nakano E, Miyata M, Tsujikawa A. Analysis of Retinal Nerve Fibre Thickening in Progressive and Non-progressive Non-arteritic Anterior Ischaemic Optic Neuropathy Using Optical Coherence Tomography. Neuroophthalmology. 2020 Jun 25;44(5):307-314.
33. Kupersmith MJ, Sibony P, Mandel G, Durbin M, Kardon RH. Optical coherence tomography of the swollen optic nerve head: deformation of the peripapillary retinal pigment epithelium layer in papilledema. Invest Ophthalmol Vis Sci. 2011 Aug 22;52(9):6558-64.
34. Knox DL, Kerrison JB, Green WR. Histopathologic studies of ischemic optic neuropathy. Trans Am Ophthalmol Soc. 2000; 98: 203–220; discussion 21–22.
35. Lee GH, Stanford MP, Shariati MA, Ma JH, Liao YJ. Severe, early axonal degeneration following experimental anterior ischemic optic neuropathy. Invest Ophthalmol Vis Sci. 2014 Sep 23;55(11):7111-8.
36. Hedges TR 3rd, Vuong LN, Gonzalez-Garcia AO, Mendoza-Santiesteban CE, Amaro-Quierza ML. Subretinal fluid from anterior ischemic optic neuropathy demonstrated by optical coherence tomography. Arch Ophthalmol. 2008 Jun;126(6):812-5.
37. Savini G, Bellusci C, Carbonelli M, et al. Detection and quantification of retinal nerve fiber layer thickness in optic disc edema using stratus OCT. Arch Ophthalmol. 2006;124(8):1111–1117.
38. KaramEZ, HedgesTR. Optical coherence tomography of the retinal nerve fiber layer in mild papilloedema and pseudopapilloedema. Br J Ophthalmol. 2005;89:294–298.
39. Yan Y, Liao YJ. Updates on ophthalmic imaging features of optic disc drusen, papilledema, and optic disc edema. Current Opinion in Neurology. 2021 Feb;34(1):108-115.
40. González Martín-Moro J, Contreras I, Gutierrez-Ortiz C, Gómez-Sanz F, Castro-Rebollo M, Fernández-Hortelano A, Pilo-De-La-Fuente B. Disc Configuration as a Risk and Prognostic Factor in NAION: The Impact of Cup to Disc Ratio, Disc Diameter, and Crowding Index. Semin Ophthalmol. 2019;34(3):177-181.
41. Rebolleda G, Diez-Alvarez L, Casado A, Sánchez-Sánchez C, de Dompablo E, González-López JJ, Muñoz-Negrete FJ. OCT: New perspectives in neuro-ophthalmology. Saudi J Ophthalmol. 2015 Jan-Mar;29(1):9-25.
42. Menke MN, Feke GT, Trempe CL. OCT measurements in patients with optic disc edema. Invest Ophthalmol Vis Sci. 2005 Oct;46(10):3807-11.
43. Wang W, Liu J, Xiao D, Yi Z, Chen C. Features of peripapillary hyperreflective ovoid mass-like structures in nonarteritic anterior ischemic optic neuropathy patients and normal controls. Transl Vis Sci Technol. 2024;13(1):7.
44. Fard MA, Sahraiyan A, Jalili J, Hejazi M, Suwan Y, Ritch R, Subramanian PS. Optical Coherence Tomography Angiography in Papilledema Compared With Pseudopapilledema. Invest Ophthalmol Vis Sci. 2019 Jan 2;60(1):168-175.
45. Fraser JA, Sibony PA, Petzold A, Thaung C, Hamann S, Consortium O. Peripapillary hyperreflective ovoid mass-

like structure (PHOMS): an optical coherence tomography marker of axoplasmic stasis in the optic nerve head. J Neuroophthalmol. 2021;41(4):431–441.
46. Moyseyenko N. Disorders of aqueous humor flow in the posterior part of the eye in the mechanisms of optic nerve damage development (literature review). J Ophthalmol (Ukraine) [Internet]. 2023 Nov. 1 [cited 2024 Apr. 4];(5):46-52.

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