Chapter

Morphofunctional Changes of the Retina and Optic Nerve in Optical Neuropathy of Various Genesis: A Literature Review

Svetlana Zhukova, Tatiana Iureva and Dmitry Samsonov

Abstract

The retina is part of the central nervous system and has much in common with the brain's physiological characteristics. Ophthalmological manifestations often precede the symptoms of central nervous system disorders and are used for their early diagnosis. Retinal imaging is simpler and more economical than the available central nervous system imaging methods. In this connection, the search for retinal biomarkers of neurodegenerative diseases is relevant. Optical coherence tomography is highly valuable both for routine clinical practice and for research purposes. Different patterns of structural changes of the optic nerve and retina in optical neuropathies of various genesis are due to differences in the pathogenesis of diseases (glaucoma optic neuropathy, non-arterial anterior ischemic optic neuropathy, optic neuritis associated with multiple sclerosis, and compression optic neuropathy). The identified biomarkers can be used for screening patients in primary healthcare institutions to provide a preliminary diagnosis of patients at risk.

Keywords: optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), ganglion cells complex (GCC), retinal nerve fibers layer (RNFL), optic nerve, neurodegenerative diseases

1. Introduction

In the general cascade of events leading to irreversible changes in the optic nerve, damage to the nerve fiber layer, and the retinal ganglion cell complex (GCC) are important factors contributing to the optical neuropathy pathogenesis of any genesis [1–7]. The possibility of retrograde trans-synaptic degeneration of visual fibers in visual pathway central neuron damage [8] opens up new prospects for visualizing morphological changes in the central nervous system (CNS) at the retinal level, since the retina being a part of the central nervous system, has much in common with the physiological characteristics of the brain.

The organization of visual pathway neural links is quite complex. Within the retina of every eye, it is a layer of photoreceptors (I neuron), then bipolar (II neuron)

and ganglion cells with their long axons (III neuron). Together, they form the peripheral part of the visual pathway, represented by the optic nerves, chiasm and visual tracts. The visual tracts end in the cells of the corpus geniculatum laterale (CGL), which is the primary visual center. Central neuron fibers of the visual pathway (radiatio optica Gratiolet) originate from them and reach the area striate of the occipital lobe of the brain, where the primary cortical center of the visual analyzer is localized (**Figure 1**) [9].

The uniqueness of the visual pathway organization is that there is only one synapse between the retina and the visual cortex. Thus, any damage to the optic nerve head (ONH) will lead to trans-synaptic (trans-neuronal) degeneration in both anterograde and retrograde directions. Trans-synaptic anterograde degeneration leads to changes in the CGL, radiatio optica, and visual cortex, and trans-synaptic retrograde degeneration leads to changes in the retinal ganglion cell complex (GCC) (**Figure 1**) [10, 11].

Ophthalmoscopic manifestations of neurodegenerative diseases often precede the symptoms of CNS disorders and are used for their diagnosis. In turn, retinal visualization is much simpler and more economical than the available methods of CNS visualization.

The most technologically advanced and dynamically developing imaging method in ophthalmology is optical coherence tomography (OCT). Qualitative assessment

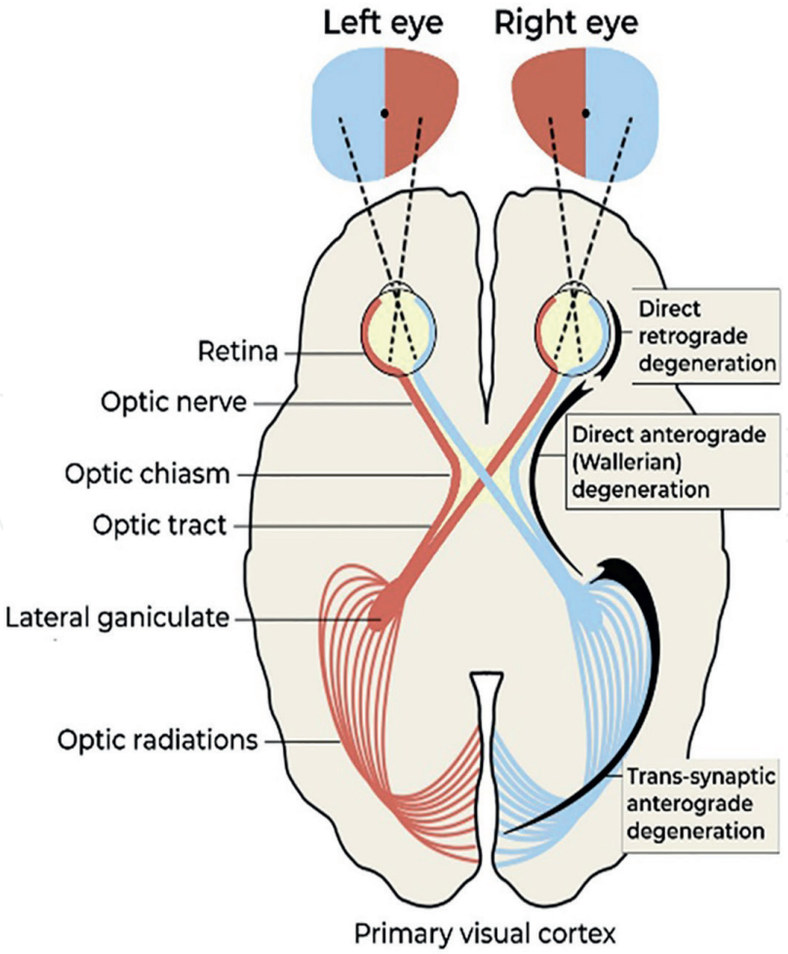

Figure 1.
The structure of the visual pathway.

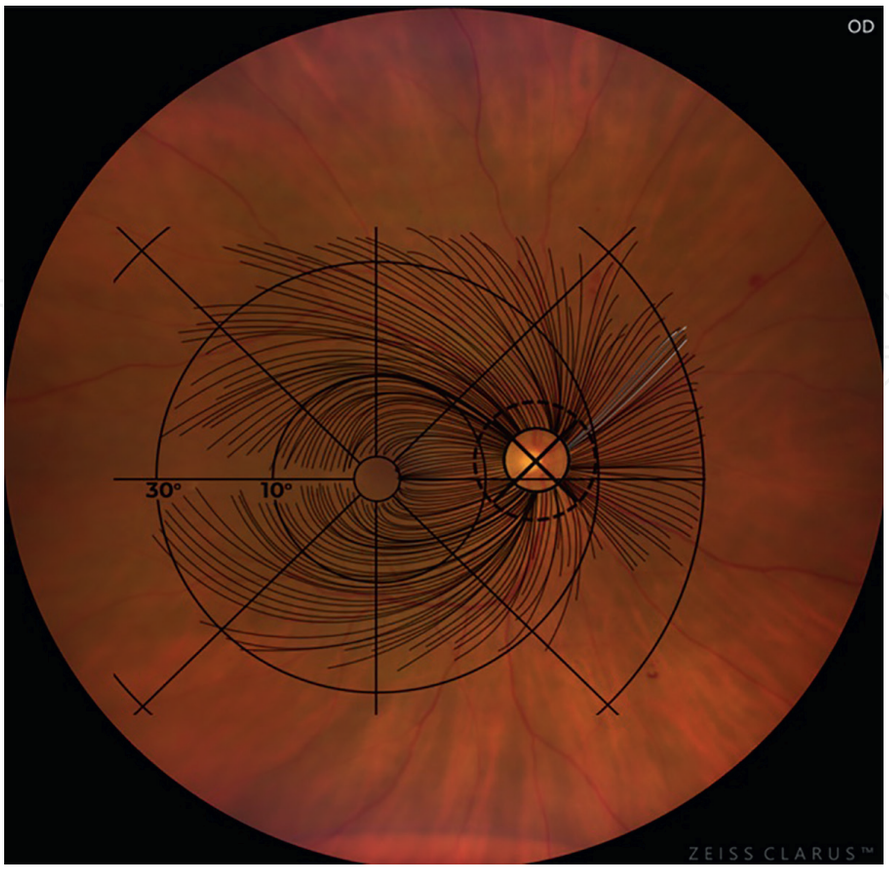

Figure 2.
Retinal nerve fiber layer topography.

and quantitative analysis, integrated into the tomography software, allow identifying pathological changes in the studied structures with high repeatability and specificity.

When evaluating OCT images, it is necessary to understand the factors that determine the structural changes' range. The topography of the retinal nerve fibers layer (RNFL) is characterized by strict regularity. Ganglion cell axons extending from the central retinal region, as a part of the papillomacular bundle, form the temporal part of the ONH. Fibers extending from the superior-temporal and inferior-temporal retinal quadrants form the superior-temporal and inferior-temporal segments, respectively. Axons extending from ganglion cells located nasally and along the retinal periphery penetrate into the optic nerve disc from the nasal side. From the periphery of the temporal part of the retina, axons are directed to the superior and inferior parts of the ONH (**Figure 2**) [12].

Various patterns of damage to the RNFL and GCC are caused by the pathogenesis of neurons' primary damage. These differences can be used as differential diagnostic criteria for glaucomatous and non-glaucomatous optical neuropathies in routine clinical practice.

2. Glaucoma optic neuropathy

Primary open-angle glaucoma is a chronic progressive optical neuropathy resulting from damage to retinal ganglion cells [13, 14]. Damage to the GCC axons in glaucoma is initialized in the optic nerve head by various mechanisms, such as mechanical

compression of intraocular pressure, vascular disorders, immunological influence, and oxidative stress. This can lead to direct retrograde damage to the GCC, followed by thinning of the RNFL and visual field defects [15].

A comprehensive assessment of early-onset glaucoma and its subsequent monitoring is achieved by combining the results of "structure-function." The key diagnostic methods for glaucoma are OCT and static automated perimetry (SAP). Each of the methods has its advantages and limitations.

Structural and functional relationships reach their peak at the advanced stage of the disease [16]. At early and late stages of glaucoma, there may be contradictions between OCT and SAP [17–20].

OCT allows for obtaining objective information about the retinal layers' thickness with high repeatability and reproducibility. Diagnostic OCT markers of POAG are the width of the rim area, RNFL, and GCC thickness [21, 22].

The temporal half of the superior and inferior quadrants of the optic nerve head are the most vulnerable areas of peripapillary RNFL loss—the superior and inferior vulnerable zones (superior vulnerable zone—SVZ & inferior vulnerable zone—IVZ) [23–25]. In severe glaucoma, the values reach a "floor effect" level [26].

With the progression of glaucoma, the defects area increases. With a decrease in the thickness of the RNFL and GCC to the "floor" level (50–70% of the nerve fiber layer thickness of healthy eyes), the existence of functional axons in the remaining layer is assumed, but the total number of these axons does not significantly contribute to the thickness of the layer [16, 27].

Nevertheless, the papillomacular bundle and high central vision in glaucoma patients persist until the later stages of the disease. The inferior macular zone associated with arcuate defects of peripapillary nerve fibers is more vulnerable, therefore, in the late stage of the disease, asymmetric preservation of the macula is often observed.

At the same time, in early glaucoma, SAP may not be informative, because statistically significant visual field defects are detected with 25–35% loss of retinal ganglion cells [28]. Visual field defects are not detected in the early stages due to the inability of the SAP to detect small functional losses as a result of the redundancy of the visual system and the overlap of receptive fields [29]. In addition, the SAP method is subjective, high concentration is required from the patient during the study, which can reduce the repeatability and reproducibility of testing.

The software of modern computer perimeters provides wide opportunities for analyzing threshold values of retinal photosensitivity. Thus, sensitivity to early glaucoma changes increases with cluster analysis, when the test points of the visual field are located and grouped along the course of a single bundle of retinal nerve fibers (clusters). The mean cluster photosensitivity defect is calculated for every cluster (**Figure 3**) [30, 31].

In addition to cluster analysis, anatomically oriented polar analysis is carried out in the Octopus perimeter [32]. It provides information about the expected location of morphological lesions of the rim area in the optic nerve head. Each visual field defect is combined with a nerve fibers bundle that hypothetically corresponds to it. Then, a vector is applied to the diagram of the optic nerve head at a certain angle corresponding to the localization of the defect, the length of which reflects the loss of photosensitivity in dB (**Figure 3**).

The addition of central test points to Protocol 24-2, 30-2, and macular area testing (Protocol 10-2) increases the effectiveness of testing [33].

To compare structural and functional defects, RNFL and GCC thickness maps can be superimposed on the test points of the visual field (24-2 location on the FNFL thickness map and 10-2 on the GCC thickness maps) (**Figure 4**).

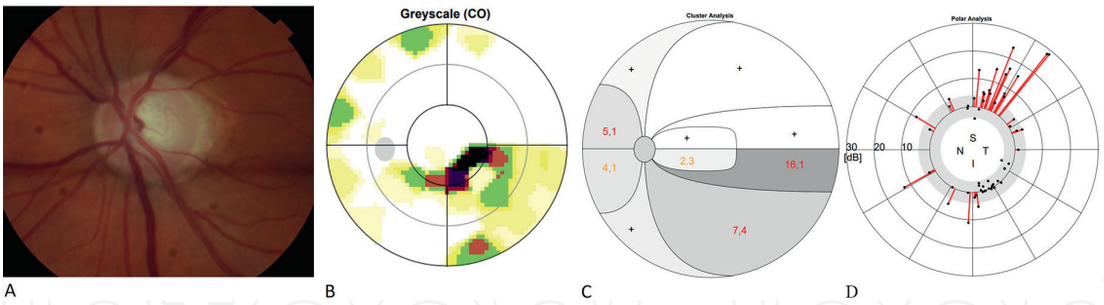

Figure 3.
54-year-old man with glaucoma. A—fundus-image. B—grayscale of values. The color scale indicates the absolute values of the light sensitivity thresholds in the form of a color map. C—cluster analysis. The degree of background darkening reflects the degree of deviation of clusters from the norm. D—polar analysis. The gray sector is in the normal range. The red vector is the radial coordinate. The length of the vector indicates the length of the defect. The angular coordinate is determined by the entry angle of nerve fibers bundles connected to each test point in the optic nerve disk.

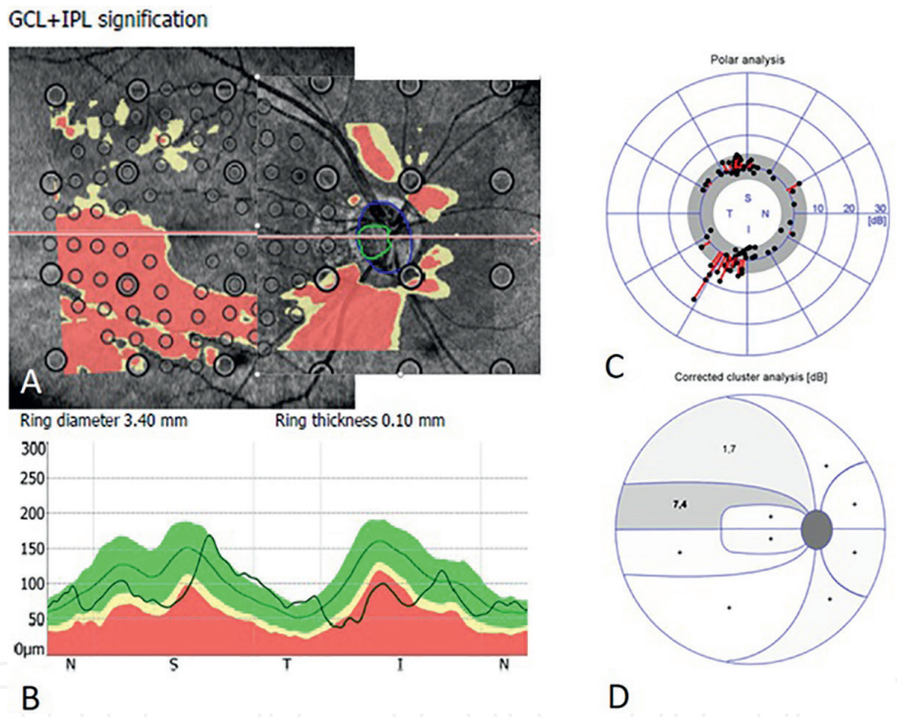

Figure 4.
Spatial correspondence of structural-functional indicators. A 48-year-old man with glaucoma. BCVA 1.0. A—superposition of abnormal points of the visual field on RNFL and GCC probability maps (Revo NX, Optopol). B—NSTIN-RNFL profile color-coded. C—polar analysis. D—cluster analysis.

A better understanding of the spatial correspondence of structural-functional indicators is facilitated by the representation of the profile of the peripapillary nerve fibers layer in the form of a scan graph NSTIN (nasal, N; superior, S; temporal, T; inferior, I; nasal, N), when the indicators of the RNFL thickness from the temporal half of the disk are presented in the middle of the graph (**Figure 4**) [34].

The evolution of OCT in ophthalmology has led to the emergence of a fundamentally new research method—OCT angiography (OCTA). OCTA is a new method of noninvasive visualization of blood vessels in the ONH and retina *in vivo* [35, 36].

Localized RNFL defects are spatially associated with density reduction of peripapillary vessels, even in early and preperimetric glaucoma. The most pronounced differences in OCTA indices between groups of healthy individuals and glaucoma patients were found in the inferior-temporal and superior-temporal quadrants of the peripapillary retina. Thus, the relationship between structural and functional, and hemodynamic changes in patients with POAG is obvious (**Figure 5**) [37, 38].

At the same time, multifunctional correlations are stronger than structural-functional ones [39].

Thus, the OCTA method is promising and, along with structural OCT and visual field testing, can become part of everyday routine practice. Today, OCTA is successfully used in the primary diagnosis of glaucoma, differential diagnosis of glaucoma in combined pathology, disease monitoring, and hemodynamic shifts assessment in IOP fluctuations [40, 41].

The characteristic pattern of RNFL and GCC damage in glaucoma is asymmetric paracentral macular defects associated with arcuate defects of the peripapillary RNFL, corresponding to them a density reduction of the peripapillary and parafoveolar capillaries, and perimetric defects.

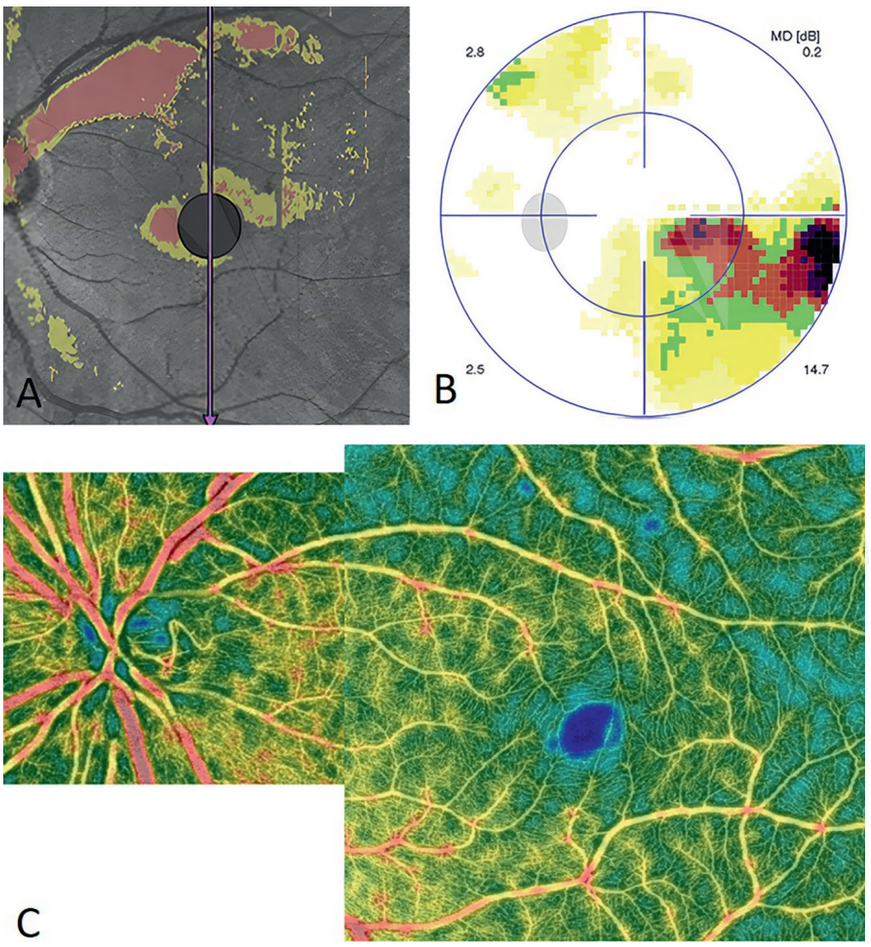

Figure 5.
54-year-old man with advanced glaucoma. BCVA 1.0. A—OCT probability map of RNFL and GCC. B—grayscale of values. C—OCTA, capillary density of the radial peripapillary plexus and the superficial plexus. A significant decrease in the peripapillary and parafoveolar capillaries density, corresponds to the thinning of GCC and RNFL.

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3. Non-arterial anterior ischemic optic neuropathy

Non-arterial anterior ischemic optic neuropathy (NAION) is the second most common optical neuropathy after glaucoma optic neuropathy (GON) among middle-aged and older people caused by hypoperfusion in the posterior short ciliary arteries that supply blood to the ONH [42–44].

The pathogenesis of NATION is not fully known. However, anatomical predisposition, narrow scleral canal, optic disc druses, systemic hypertension, diabetes mellitus, cardiovascular diseases, and hypercholesterolemia are risk factors for NAION [45]. Ischemic damage to the optic nerve head triggers a vicious circle of increasing ischemia. Hypoxia of axons of ganglion cells blocks axoplasmic current and leads to edema of the ONH. The optic nerve is quite rigid, so axons can expand only due to the compression of surrounding tissues (the mechanism of compartment syndrome). Compression of capillaries and smaller vessels increases axonal hypoperfusion, which, in turn, leads to further axoplasmic stagnation and edema [46, 47].

Diagnosis of NAION in the acute phase with painless loss of vision for several hours or days, ONH edema does not cause difficulties. In the chronic stage, it can be

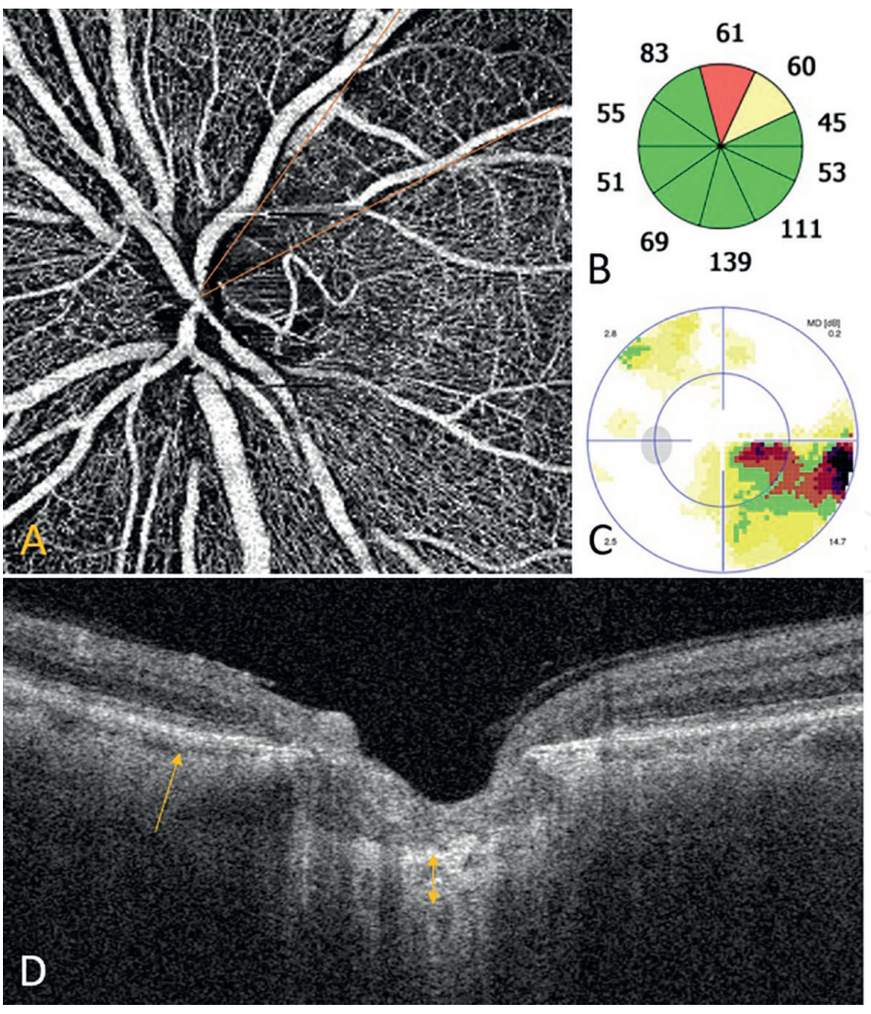

Figure 6.
48-year-old man with GON. A—OCTA*, radial peripapillary plexus, B—a graph of RFNL thickness, C—grayscale of values, D—ONH b-scan and peripapillary retina.*

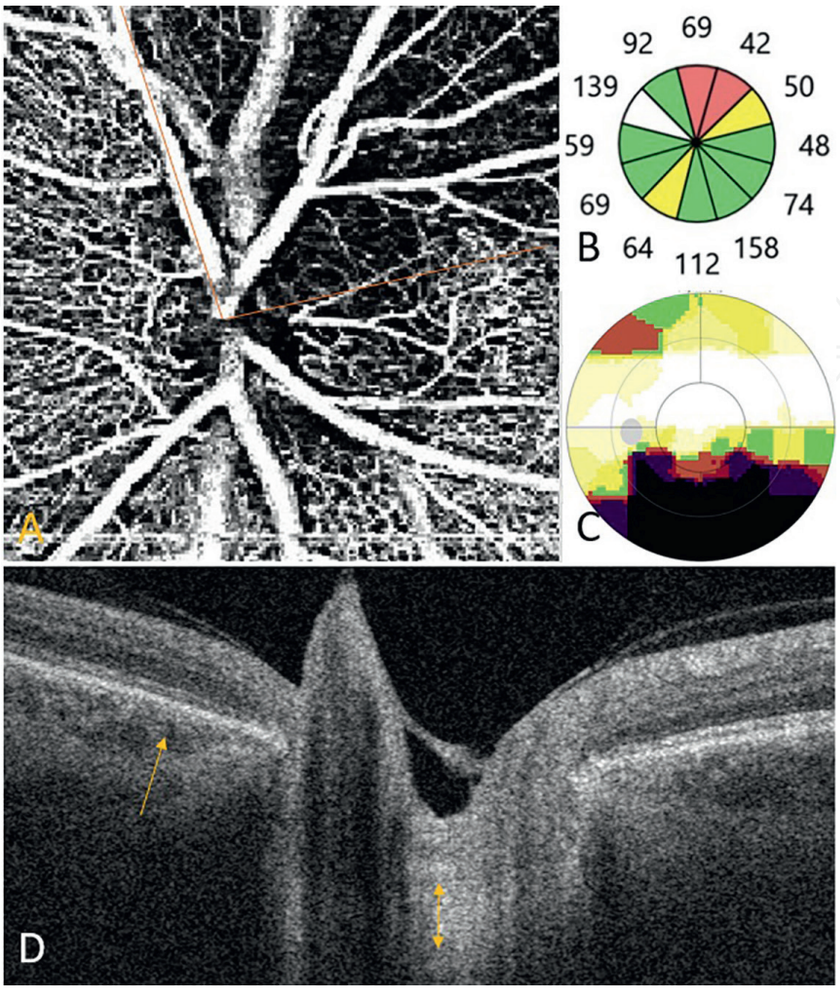

Figure 7.
42-year-old man with NAION. A—OCTA, *radial peripapillary plexus, B—a graph of RFNL thickness, C—grayscale of values, D—ONH b-scan and peripapillary retina.*

difficult to differentiate NAION from GON, since the pattern of RNFL loss and visual field defects may be similar (**Figures 6** and 7).

Despite the comparable thickness of the nerve fiber layer in both patients, a patient with NAON has a more diffuse decrease in peripapillary capillaries and a more pronounced depression of the visual field, a greater thickness of the peripapillary choroid and the lamina cribrosa.

The importance of differential diagnosis is due to different prognosis and treatment approaches. There are no effective methods of NAION therapy. Treatment is reduced to the elimination of vascular risk factors to prevent the occurrence of the disease in the paired eye [48]. Therefore, a correct diagnosis will prevent unnecessary excessive treatment that is prescribed due to incorrect diagnosis of NAION as glaucoma.

Similar to glaucoma, NAION also leads to the loss of ganglion cells and damage to the RNFL in the superior and inferior quadrants. However, in contrast to GON, in NAION the damage to the RNFL in the superior and inferior quadrants is more diffuse (from the temporal to the nasal edge) (**Figure 7**). Defects of the RNFL in the superior quadrant are formed more often. The superior-nasal segment is the most vulnerable [6, 49, 50].

Different patterns of RNFL and GCC damage reflect different patterns of primary damage to neurons and indicate different mechanisms of vascular disorders in each condition. In GON, changes in the form of arc-shaped defects are consistent with the topography of retinal nerve fibers [51]. In turn, in NAION, the changes are due to the structure of the Zinn-Haller arterial vascular circle, which is formed by the distal branches of the posterior short ciliary arteries and consists of the lower and upper halves [52].

Obviously, the changes in both retinal and choroidal peripapillary blood flow will be different. The decrease in the density of the capillaries of the radial peripapillary plexus in NAION is more pronounced than in GON [53]. A thicker peripapillary choroid is a predisposing factor for the development of NAION [54–56]. Unlike GON, capillary perfusion of the prelaminar tissue induces axonal damage without deformation and damage to lamina cribrosa [57].

Thus, the state of the choroid and lamina cribrosa can be additional differential diagnostic criteria of GON and NAION.

4. Optic neuritis associated with multiple sclerosis

Optic neuritis associated with multiple sclerosis: Multiple sclerosis (MS) is a chronic neurodegenerative disease characterized by demyelination of various parts of the central nervous system caused by (autoimmune) inflammatory processes.

Optic neuritis (ON) is an initial symptom in about 20% of MS patients and occurs in 50% of patients during the course of the disease [58].

The pathological mechanism underlying the decrease in the thickness of RNFL and GC in patients with MS, both with and without previous ON, still remains controversial. However, it is recognized that progressive structural changes are caused by neurodegeneration, not inflammation [59]. There is a correlation between the OCT parameters and the MS manifisattions. RNFL and GCC thinning associated with optical neuropathy in MS correlate not only with visual acuity, and the rate of progression of the disease but also with a lesion of the gray matter of the brain. Therefore, OCT is used to monitor the disease, potentially reducing the need for frequent magnetic resonance imaging [60–64].

The changes in the GCC in MS are ahead of the RNFL changes. Volume and thickness analysis GCC is a more sensitive and reliable indicator of retrobulbar neuroaxonal damage in MS (appears on average after 2 weeks) [3].

The temporal quadrant of the RNFL is more sensitive to damage (**Figure 8**). Lower RNFL values correlate with a decrease in visual acuity, contrast sensitivity, average sensitivity of the visual field, and average indicators of color vision [65].

OCTA demonstrates a decrease in the density of parafoveolar and peripapillary capillaries, respectively, structural damage.

The detection of changes in the paired eye without ON reflects subclinical structural damage of the RNFL. Performing OCT is advisable for monitoring the disease, predicting after relapses of ON, and evaluating the effectiveness of treatment.

Despite the fact that the average thickness of the RNFL and GCC on both sides is within the normative values, the indicators on the right are lower. Local thinning of RNFL (sector 9 h) and GCC by the course of the papillomacular bundle, a decrease in the density of the parafoveolar and peripapillary capillaries along the course of the papillomacular bundle. Diffuse depression of the visual field, central perimetric defect.

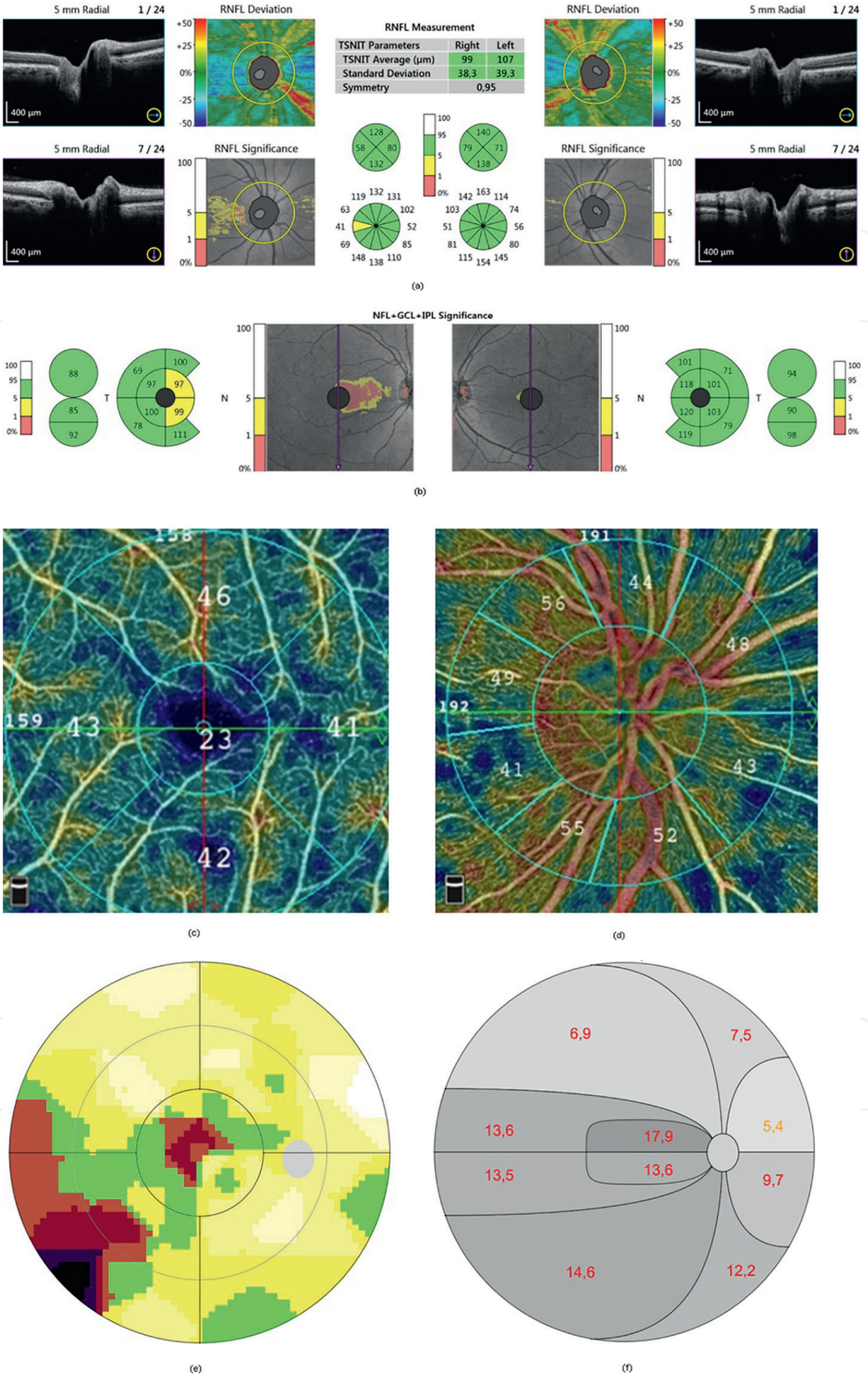

Figure 8.
Man, 42 years old. The MS debut. BCVA 0.5/1.0. A—3D scanning protocol of the OND. B—3D macular scanning protocol. C—OCTA of the superficial plexus and radial peripapillary plexus of the right eye. E—grayscale of values OD. F—cluster analysis OD.

5. Compression optic neuropathy

Compression optic neuropathy (CON) develops more often as a result of compression at the level of the optic nerve (meningioma), orbit (thyroid disease), and anterior segment of the visual pathway (more often at the level of chiasm in pituitary lesions).

If the visual pathway is affected, atrophy can go in the antegrade direction. Experimental studies have proved the existence of retrograde trans-synaptic degeneration of the visual pathway in animals [66, 67].

It was believed that with acquired damage to the central neuron of the human visual pathway, atrophy of the nerve fiber ends at the level of synapses in the external cranial body and does not extend to the anterior segment of the visual pathway [68]. Contrary to this opinion, OCT demonstrates the possibility of the existence of acquired trans-synaptic retrograde degeneration of nerve fibers of the human visual pathway [69, 70]. OCT plays a role not only in the diagnosis and monitoring of compression but also in the prediction of visual functions after surgical treatment.

CON may be detected by OCT earlier than with ophthalmoscopy. A manifestation of the compression effect on the visual tract is the RNFL and GCC thinning. GCC thinning, as a rule, is detected earlier than RNFL changes and standard automated perimeter changes. Hemianopia on perimetry can present as a hemi-macular atrophy on the OCT (**Figure 9**). The excavation increase during compression is due to antegrade degeneration of axons and secondary collapse of glial support tissue [71]. The excavation is usually rounded, central, and not vertically oriented, as in glaucoma (**Figure 10**).

When detecting the asymmetry of the excavation, the RNFL and GCC thickness in symmetrical IOP, OCT may be the key to localizing the compression location [25, 72–79].

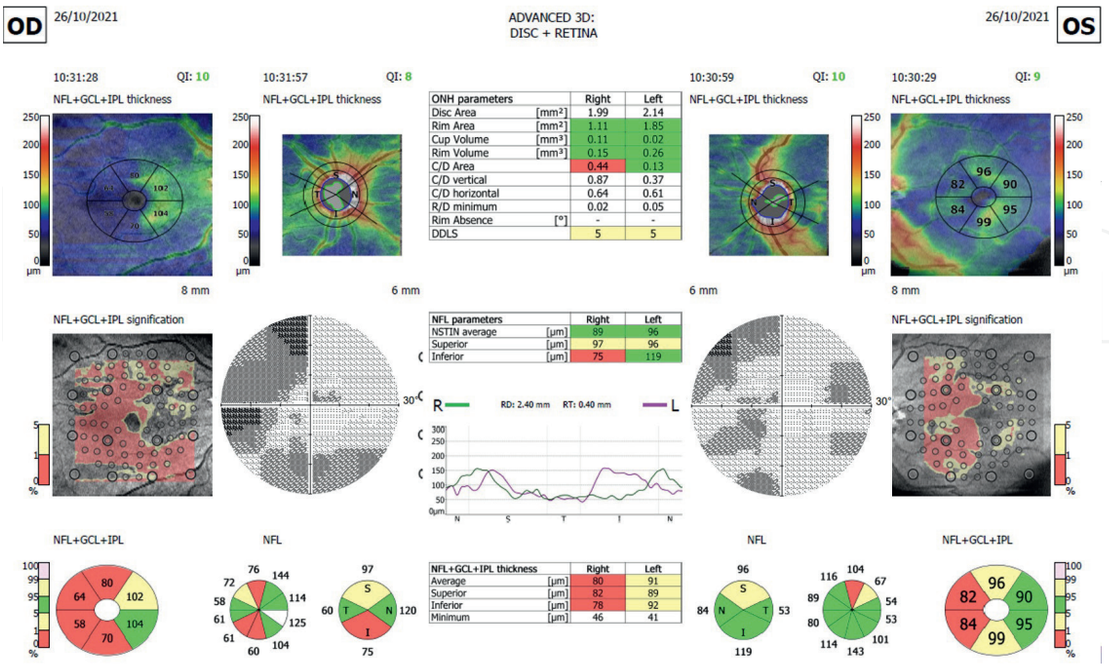

Figure 9.
A 44-year-old woman complained for the first time of a vision reduction in her right eye. BCVA 0.6/1.0. For half of the year, frequent headaches occur. A hemi-muscular atrophy on the OCT, hemianopia on perimetry. Homonymous hemianopia. A neurosurgeon's examination revealed pituitary craniopharyngioma.

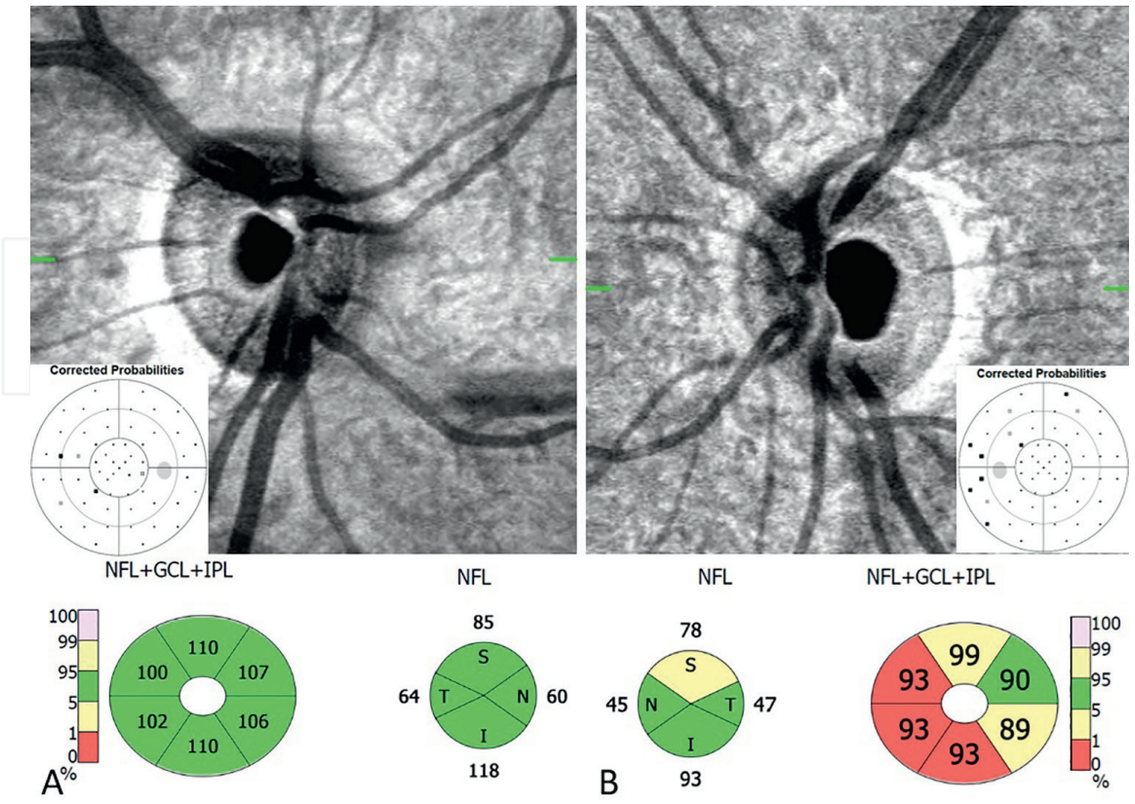

Figure 10.
A 15-year-old girl. Optic nerve glioma of OS (prechiasmal localization, external and internal hydrocephalus. BCVA 1.0/0.9. Increased excavation, RNFL and GCC thinning, and unilateral hemianopsia OS (enface optical disk, perimetry, thickness of SNVS and ganglion complex OD—A and OS—B).

Thus, the specific features of CON are decreased visual acuity, vertical defects of the visual field, decoloration of the OND, expansion of excavation, and hemi-macular atrophy on the OCT, age younger than 50 years.

The characteristic pattern of RNFL and GCC damage in optical neuropathies makes it easier to understand the various pathological mechanisms of damage and differentiate early glaucoma changes from other optical neuropathies.

Arcuate inferior temporal defects are a sign of early glaucoma ascending atrophy. Diffuse horizontally oriented loss of RNFL and GCC is a sign of ascending atrophy in NAOIN. Centrally oriented lesions of RNFL, GCC, and visual field defects are formed with descending/ascending atrophy in MS. Homonymous, vertically oriented loss of RNFL and GC is characteristic of descending atrophy in cerebral pathology in the chiasm region.

6. Conclusion

The pattern of changes in RNFL and GCC allows for predicting changes in the visual field and can be used to quantify lesions of the visual pathway in patients with brain dysfunction when it is impossible to perform perimeter tests. The high repeatability and reproducibility of objective retinal biomarkers, and ease of visualization explain the attractiveness and prospects of OCT.

Obviously, OCT is not the only tool for the diagnosis of neurological diseases; however, it can be successfully used in complex diagnostics, often replacing expensive

invasive studies. This reduces the burden on patients on the one hand and reduces healthcare costs on the other hand.

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