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DIABETIC RETINAL NEURODEGENERATION MIMICKING GLAUCOMATOUS OPTIC NEUROPATHY (CLINICAL CASE)

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Abstract
The article presents a clinical case of a 57-year-old patient with a long history of type 2 diabetes mellitus (T2DM) and chronic decompensation of glycemic control. A distinctive feature of this case is the presence of pronounced diabetic retinal neurodegeneration (DRN), which, in its structural and visual characteristics, mimicked glaucomatous optic neuropathy despite normal intraocular pressure levels.
Using multimodal diagnostic methods, including optical coherence tomography (OCT), OCT angiography, and automated perimetry, diffuse symmetrical thinning of the retinal nerve fiber layer (RNFL) and the ganglion cell complex (GCL++) was identified, along with an increase in the optic disc excavation. However, the absence of sectoral defects, the preservation of the neuroretinal rim according to the ISNT rule, and the specific nature of functional changes allowed for the exclusion of glaucoma and the verification of DRN as an independent pathogenetic factor. This case emphasizes the need for a differentiated approach to interpreting OCT data in patients with long-standing diabetes to prevent the overdiagnosis of glaucoma.

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Introduction

According to traditional concepts, diabetic retinopathy (DR) is considered a predominantly microvascular complication of diabetes mellitus, and microaneurysms, hemorrhages, macular edema, and neovascularization are considered key markers of progression. However, studies of recent decades convincingly demonstrate that retinal neurodegeneration is an early and independent component of diabetic damage, which can precede the clinical signs of microangiopathy [1]. In experimental animals and in postmortem tissues of patients with diabetes mellitus, ganglion cell apoptosis, reactive gliosis, decreased functional activity of neurons, and structural thinning of the inner retinal layers have been found even before the appearance of typical signs of DR [2, 3].

The current understanding of diabetic retinal neurodegeneration (DRN) includes a complex of changes: ganglion cell death, thinning of the retinal nerve fiber layer (RNFL), thinning of the ganglion cell complex and inner plexiform layer (GCC/GC-IPL), impaired neurovascular coupling, and Müller cell dysfunction. Multicenter clinical studies using spectral-domain optical coherence tomography (OCT) have shown that in patients with type 1 and type 2 diabetes mellitus, even in the absence of minimal DR, significant thinning of the inner retinal layers is already recorded compared to the control group [4, 5, 6]. These structural changes correlate with the duration of diabetes, the quality of glycemic control, and lipid levels, and frequently precede the decline in central vision [7].

Particularly important for clinical practice is the fact that the targets of diabetic neurodegeneration are the same structures traditionally used as key biomarkers of glaucoma. The OCT parameters of the RNFL and GCC layers were initially developed for the early diagnosis of glaucoma and pre-glaucomatous conditions; it is largely by the degree of their thinning that the presence and progression of the glaucomatous process are judged [8]. However, in patients with long-standing diabetes mellitus, similar thinning of the RNFL and GCC may be due to diabetic

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neurodegeneration rather than primary open-angle glaucoma. In addition, changes in the optic nerve head (ONH) as a result of diabetic neurodegeneration deserve special attention: reduction of the neuroretinal rim may occur, especially in the superotemporal sector, and the tendency to form a glaucoma-like vertical elongation of the cup increases. All this creates a risk of false-positive interpretation of a 'glaucoma-like' picture during OCT analysis without taking into account the systemic context and the features of diabetic retinal damage.

A number of studies have shown that in patients with type 2 diabetes mellitus without clinical signs of DR, the peripapillary RNFL and macular GCC are statistically significantly thinner than in healthy individuals of the same age, while these patients do not have glaucoma [9, 10]. In longitudinal observations, progressive thinning of the RNFL/GCL has been noted as a potential biomarker and pharmacological target of DR, with the neurodegenerative component potentially developing independently of the severity of vascular changes [7]. Moreover, some studies indicate that diabetes mellitus itself and its duration can be risk factors for more pronounced RNFL thinning, which theoretically increases the probability of both the presence of true glaucoma and its simulation due to diabetic neuropathy [9].

The situation is further complicated in the later stages of DR and after panretinal laser photocoagulation (PRP). Studies demonstrate that in patients who have previously undergone PRP, the RNFL layer is significantly thinner, and the optic nerve head is more often assessed as 'abnormal' and frequently resembles a 'glaucomatous' ONH both on ophthalmoscopy and optical coherence tomography [11]. As a result, a wide range of glaucoma-like changes is formed in patients with long-standing diabetes mellitus—from isolated RNFL/GCC thinning and suspicious visual field defects to changes in disc shape, which may be a consequence of retinal neurodegeneration and previous treatment, rather than primary glaucoma.

Thus, retinal neurodegeneration in long-standing diabetes mellitus is capable of mimicking glaucoma at all levels—structural, functional, and even clinical-visual—which significantly complicates the differential diagnosis and management of such patients. An error in interpreting OCT and perimetry data

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can lead to both the overdiagnosis of glaucoma and the unnecessary escalation of hypotensive therapy, and conversely, to the underestimation of diabetic neurodegeneration as an independent pathogenetic factor.

The recognition of DRN as a distinct pathophysiological component of DR is of fundamental importance for the development of individualized monitoring and treatment strategies. Structural changes in the inner retinal layers (RNFL, GCC/GC-IPL) detected by OCT and OCT angiography are currently considered independent predictors of functional deterioration that do not always coincide with the classical vascular stage of DR [12, 13]. The present clinical case illustrates a neurodegenerative-dominant phenotype of diabetic retinal damage in a patient with a long history of type 2 diabetes mellitus, in whom pronounced changes in the inner retinal layers and RNFL mimicked a glaucomatous process and significantly complicated both the diagnosis and the choice of further management tactics.

Objective of the study:

To present a clinical case of diabetic retinal neurodegeneration clinically and structurally mimicking glaucomatous optic neuropathy, and to demonstrate key differential diagnostic features that allow distinguishing these conditions and avoiding diagnostic and therapeutic errors.

Case Report

Patient Sh., 57 years old, with a 15-year history of type 2 diabetes mellitus, has been stably decompensated over the last few years (glycated hemoglobin HbA1c > 9%). This is a significant fact since, according to several researchers, prolonged hyperglycemia is a key factor in the neurodegeneration of the inner retinal layers [12, 14].

On admission, the patient complained of a gradual decrease in near vision, which is quite often observed in individuals of his age and rarely attracts attention. The patient also noted quite frequent photopsias and a decrease in image clarity in low light. We regarded this complaint as a sign of inner retinal layer dysfunction, as well as a decrease in contrast sensitivity.

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Upon objective examination, the best-corrected visual acuity was: OD – 0.9; OS – 0.8, i.e., an insignificant bilateral decrease in central vision without pronounced asymmetry. According to Chhablani J. et al., in DRN, the decrease in vision is not associated with macular thickness, but is caused by the loss of ganglion cells [15].

Goldmann applanation tonometry showed 14 mmHg in OD and 13 mmHg in OS, which convincingly indicates a normotensive level of intraocular pressure (IOP). In our opinion, this was a critically important factor since the subsequent structural changes in the RNFL layer and the optic nerve head could have been mistakenly interpreted as glaucomatous.

The evaluation of the anterior segment revealed the following signs: decreased corneal sensitivity, which may indicate diabetic peripheral neuropathy. Mild peripheral opacities were found in the lens. We also detected a slight slowing of the pupillary reaction to light symmetrically in both eyes, which may also be a manifestation of autonomic neuropathy.

Funduscopy revealed no signs of DR; however, a fairly deep and wide excavation of the optic nerve head was visualized. This required the mandatory performance of perimetry and optical coherence tomography.

For the structural analysis of the retina and ONH, a multimodal DRI OCT Triton (Topcon) utilizing Swept Source technology with a wavelength of 1050 nm was used. This provided deep penetration and high detailing of the retinal and ONH structures, due to the high scanning speed (up to 100,000 A-scans per second). This allowed obtaining high-resolution images. The structural analysis of macular OCT is presented in Table 1.

The results of the structural macular OCT demonstrate the absence of macular edema; the retinal pigment epithelium (RPE) and outer segments of the photoreceptors are intact, and therefore, there is no classic diabetic maculopathy. However, foveal thickness is less than the age norm, which can be regarded as foveal thinning without edema, consistent with the data of several researchers. Furthermore, our patient exhibits macular thinning independent of the DR stage [14, 16].

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A study by van Dijk HW et al. demonstrated that the ganglion cell layer (GCL) is the earliest layer affected in diabetes mellitus, even before the appearance of microvascular signs of DR [17]. Thinning of the GCL++ complex, i.e., the ganglion cell layer and the retinal nerve fiber layer in the macular zone, reflects a diffuse neuronal reduction characteristic of diabetic neurodegeneration, rather than glaucomatous sectoral damage. Thinning of the RNFL in the macular zone indicates dysfunction and damage to the axons of ganglion cells. Just as in the GCL++ layer, the changes here are diffuse, which is characteristic of diabetes mellitus, not glaucoma [18].

Below is the structural analysis of the optic nerve head in the observed patient (Table 2).

The results presented in Table 2 indicate that the dimensions of both ONHs are close to the average dimensions, which means they cannot have a large excavation. Both the vertical (0.70/0.69) and linear ratio of the ONH to excavation (0.77/0.71) look suspiciously large and give grounds to suspect glaucoma. However, the area and volume of the neuroretinal rim relative to the ONH are proportionally reduced in both eyes and have a diffuse, not sectoral, nature. Literature sources emphasize that glaucoma is characterized by an asymmetry in the cup-to-disc ratio of >0.2 between fellow eyes, and the reduction of the neuroretinal rim has a sectoral nature, while in systemic neuropathies and diabetic neurodegeneration, symmetric and diffuse thinning without pronounced asymmetry between fellow eyes is more often observed [19, 20, 21].

As demonstrated above, the analysis of the patient's optic nerve heads revealed a bilateral symmetric increase in excavation while maintaining a relatively uniform neuroretinal rim without local notches. The area and volume of the rim are diffusely decreased in both eyes (rim area 0.66 – 0.70 mm²), which is combined with a moderate diffuse thinning of the RNFL and GCL according to OCT data. The classic ISNT/IST rule is formally violated; however, the distribution pattern of the rim thickness and RNFL does not correspond to the glaucomatous profile: there is no isolated thinning of the inferior or superior sector, no local notching is detected, and the structural changes have a systemic, symmetric nature.

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OCT angiography of both eyes revealed signs of microcirculatory dysfunction at the level of the macular zone, without evidence of focal ischemia or neovascularization. In the superficial capillary plexus, a heterogeneous capillary network with areas of reduced perfusion density parafoveally is noted, as well as irregularity in the contours of the foveal avascular zone (FAZ). At the level of the deep capillary plexus, local zones of hypoperfusion, a mosaic vascular pattern, and signs of decreased capillary density are visualized, which is a characteristic marker of early impairment of neurovascular coupling in diabetes mellitus.

The patient presents a diffuse decrease in light sensitivity without characteristic glaucomatous defects. According to automated perimetry data, irregular, scattered areas of threshold depression were identified, predominantly pronounced in the inferonasal quadrant of each eye, but without the formation of arcuate and paracentral scotomas. The zones of sensitivity reduction in the right eye are up to -3.33 dB, and in the left eye – up to -4.61 dB, which reflects a moderate, symmetric, and non-specific functional dysfunction typical for retinal neurodegeneration and atypical for glaucoma, where localized defects are expected.

Conclusion

The present work describes a clinical case of a 57-year-old patient with a long history of type 2 diabetes mellitus and chronic hyperglycemia, in whom pronounced signs of diabetic retinal neurodegeneration were noted in the absence of clinically significant vascular retinopathy and at a normal level of intraocular pressure. Despite the increase in the vertical cup-to-disc ratio up to 0.70 - 0.77 and a decrease in the thickness of the inner retinal layers according to OCT data, the structural phenotype does not correspond to glaucomatous optic neuropathy: diffuse, symmetric thinning of the retinal nerve fiber layer (RNFL), pronounced reduction of the ganglion cell complex (GCL/GCL++) with preservation of outer layers, the absence of sectoral defects of the neuroretinal rim, and violations of the ISNT rule without signs of local notching were found. The visual field analysis revealed a non-specific diffuse depression of light sensitivity without

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typical glaucomatous arcuate or paracentral scotomas, which additionally excludes glaucoma as the leading pathological process.

OCT angiography data revealed perfusion heterogeneity at the level of the superficial and deep capillary plexuses, a mosaic vascular pattern, and subfoveal reduction of the choriocapillary signal, reflecting an impairment of neurovascular coupling in diabetes mellitus. Structural, vascular, and functional impairments are completely consistent with each other and form the clinical profile of diabetic retinal neurodegeneration, which can mimic glaucomatous changes in the optic nerve head and retinal nerve fiber layer, leading to diagnostic uncertainty in patients with long-standing diabetes.

Thus, this clinical case demonstrates the importance of a comprehensive ophthalmological examination in diabetes mellitus, including OCT, GCC complex analysis, OCT angiography, neuroretinal rim assessment, and functional tests. It emphasizes the need for differentiated interpretation of structural changes in the optic nerve head, as neurodegenerative mechanisms can lead to pseudo-glaucomatous excavation and diffuse loss of ganglion cell axons without pressure-dependent neuropathy. Our observation underscores that diabetic neurodegeneration represents an independent pathological condition accompanied by impaired contrast sensitivity and reduced visual functions, requiring a distinct clinical approach that is different from the traditional glaucoma management algorithm.

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