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OPTIC NEUROPATHY AND EXOPHTHALMOS EDEMATOUS: SYMPTOM OR COMPLICATION?

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✧ The article is concentrated on the mechanism of the development of optic neuropathy in patients with edematous proptosis – one of the clinical forms of endocrine ophthalmopathy. All probable options for the pathogenesis of optic neuropathy are reviewed in detail: increased intraorbital pressure, compression of the optic nerve by enlarged extraocular muscles, the formation of the apical syndrome with compression of the optic nerve in the zone of the Zinn's ring, an increase in the volume of orbital fat, tension of the optic nerve by an anteriorly shifted eye (exophthalmos), and arterial blood flow impairment in the ophthalmic artery, impaired venous blood flow in the orbit. Based on 103 follow-ups of patients with edematous proptosis and optic neuropathy (68 of them had initial optical neuropathy), the author offers her concept of the pathogenesis of optic neuropathy in patients with sub- and decompensated edematous proptosis, considering optic neuropathy as a complication of endocrine ophthalmopathy. The signs of optical neuropathy in the initial stage of its development are conceived.

✧ ***Keywords:*** endocrine ophthalmopathy; edematous proptosis; Grave's orbitophathy; optic neuropathy.

ОПТИЧЕСКАЯ НЕЙРОПАТИЯ И ОТЁЧНЫЙ ЭКЗОФТАЛЬМ: СИМПТОМ ИЛИ ОСЛОЖНЕНИЕ?

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✧ Статья посвящена механизму развития оптической нейропатии у больных отёчным экзофтальмом — одной из клинических форм эндокринной офтальмопатии. Подробно рассмотрены все предлагаемые варианты патогенеза оптической нейропатии: повышение внутриорбитального давления, компрессия зрительного нерва увеличенными экстраокулярными мышцами, формирование апикального синдрома с компрессией зрительного нерва в зоне циннова кольца, увеличение объёма орбитальной клетчатки, натяжение зрительного нерва смещённым кпереди глазом (экзофтальм), нарушение артериального кровотока в глазной артерии, нарушение венозного кровотока в орбите. Располагая наблюдением над 103 пациентами с отёчным экзофтальмом и оптической нейропатией, из которых у 68 человек была начальная оптическая нейропатия, автор предлагает свою концепцию патогенеза этой патологии у больных суб- и декомпенсированным отёчным экзофтальмом, расценивая оптическую нейропатию как осложнение эндокринной офтальмопатии. Предложена симптоматика оптической нейропатии в начальной стадии её развития.

✧ ***Ключевые слова:*** эндокринная офтальмопатия; отёчный экзофтальм; орбитопатия Грэйвса; оптическая нейропатия.

INTRODUCTION

Knowledge on optic neuropathy (ON) in patients with endocrine ophthalmopathy (Graves' orbitopathy in the foreign literature terminology) in the presence of Graves' disease became tangible only in the late 1950s. By this time, J. Igersheimer and R. Day described peripheral scotomata in patients with endocrine ophthalmopathy (EOP) and evaluated detected

changes as an important sign of optic nerve involvement in the pathogenesis of the disease. With the advent of imaging techniques (computed tomography and magnetic resonance imaging (CT and MRI)), attention to ON has become more intense.

Incidence: From recent reports, the incidence of ON in EOP patients ranges from 3.4–8% [1–5]. In the UK, the incidence in recent years has been 0.75 per million of population per year [6]. It is reasonable to suppose that the incidence depends on the degree of compensation of thyroid-eye disease as one of the clinical forms of EOP, and with its decompensation, it reaches 75% [7].

The pathogenesis of ON remains a subject of discussion since its first description. One of the first causes was considered to be an increase in intraorbital pressure as a result of an increase in contraction of extraocular muscles (EOM) [8], compression of the optic nerve by enlarged musculi recti as a result of edema and cellular infiltration (typical of EOP) [9, 10], and priority was given to an increase in the musculus rectus inferior [11]. At the same time, it was revealed that the sizes of musculus rectus lateralis, musculus rectus superior, and musculus rectus inferior could not be considered as prognostic; meanwhile the size of the musculus rectus medialis was recognized as an important measurable predictor of ON [12].

The priority of increase in the sizes of the musculus rectus medialis, musculus rectus inferior, and obliquus superior in the pathogenesis of ON, especially at the apex of the orbit with simultaneous tension of the tarso-orbital fascia, preventing the development of "arbitrary" orbital decompression, was emphasized by O.G. Panteleeva [13]. The questions remain; why do patients with compressed optic nerve have an early visual impairment? Why is the choked disc detected rarely? While patients with an encapsulated orbital tumor with a pronounced choked disc do not experience visual impairment for many years?

Comparison of metric EOM indices in patients with edematous exophthalmos (with and without ON) according to CT and MRI confirmed the absence of significant differences in the mean volumes of the musculi recti [14]. The authors confirmed that EOMs themselves do not cause ON [15, 16]. ON in patients with edematous exophthalmos, was considered as a consequence of the apical syndrome or apical "crowding," in which, at the apex of the orbit outlet, increase in EOM volumes compress the optic nerve [17, 18]. It should be noted that one of the causes of apical "congestion" was also assumed to be the presence of inflammation and possible impaired blood circulation at the orbital apex [14].

There are controversies about the tension of the optic nerve in case of increased EOMs and exophthalmos [17, 18]. Opinions have been expressed about the dominant role of an increase in the volume of orbital tissue in the development of ON as a result of its hypertrophy [19, 20]. However, our study using CT and MRI explorations of EOP patients with ON [10, 14, 21, 22], did not confirm this opinion. Several reports claim that the vascular component (the retinal microcirculation disorder) is the primary component in the pathogenesis of ON. Microcirculation disorders in the retina and the primacy of its impairment is proven and considered as one of the important links in the mechanism of visual impairment in patients with edematous exophthalmos and ON [23]. Subsequently, a decrease in the blood flow velocity in the ophthalmic artery and its branches was considered to be the cause of ischemia [5]. The color Doppler imaging demonstrated decrease in the flow velocities of the internal carotid artery, ophthalmic and central retinal arteries in ON patients [5]. However, the authors associated the detected decrease in arterial blood flow with "inflammatory lesion" of the orbital soft tissues leading to hypoxia and damage to the optic nerve. O.G. Panteleeva et al. [24] paid attention to the impairment of blood flow in the ophthalmic artery territory in patients with edematous exophthalmos complicated with ON. The authors believe that the first step in the development of ON is retinal ischemia caused by decrease in the blood flow velocity of the ophthalmic artery branches. Meanwhile, on analyzing this version of ON pathogenesis, many questions remain unresolved. The blood flow in the arterial system of the orbit and the eye deteriorates, but vision in such patients decreases gradually. As a rule, it improves significantly in the course of drug therapy. Is this possible with arterial insufficiency in the central artery system of the retina? No. In 2018, P. Saeed suggested that the ON pathogenesis is most likely multifactorial and it entails compression of the optic nerve by enlarged external muscles of the eye, stretching of the optic nerve under the influence of exophthalmos, increasing intraorbital pressure, causing vascular insufficiency and inflammation of the orbital soft tissues [25]. However, it was previously demonstrated using sufficient clinical material that half of EOP patients have no significant correlation between the activity of the pathologic process and ON [22]. In our opinion, such discrepancies can be explained by the variability of the bony orbit structure, as it can be wide and short or narrow and long. Moreover, the volume of the orbit of an

adult is also quite variable (18.9–33.4 cm^3), and its variability is significant, ranging from 0.25–0.4 [26–28].

The superior ophthalmic vein (SOV) as the main venous collector of the orbit (does not normally exceed 2 mm), is recognized as the most vulnerable area affected by compression due to increase in the soft tissue contents of the orbit. An increase in its diameter in edematous exophthalmos patients with concomitant ON has been elucidated by CT studies. The obstruction of blood flow in the SOV in patients with EOP and ON was first described in 1994 [29]. In such patients, it is expanded and may be clearly differentiated on CT scans [30–32]. The venous outflow deterioration is also shown by an increase in episcleral venous pressure in patients with edematous exophthalmos complicated with ON [33]. Moreover, a higher episcleral venous pressure is noted in the inferior temporal quadrant of the eye at the subcompensation phase of edematous exophthalmos [34].

Optical coherence tomography, performed in patients such patients, demonstrates the decrease in the thickness of the peripapillary layer of retinal nerve fibers in the lower area, and the more pronounced it is, the longer the ON history will be [35]. As the time of progression of ON increases, the vascular density decreases, especially in the peripapillary region of the temporal zone [36]. Such changes in the retina are accompanied by visual acuity impairment [35, 37].

Combining the above concepts of ON pathogenesis in EOP patients with the anatomical aspects of the bony orbit and its vascular system enables us to propose the following mechanisms of ON development in patients with sub- and decompensated edematous exophthalmos:

The initial stage is known as the **difficulty of venous outflow** from the orbit in the zone of the superior orbital fissure caused by increased EOM. Blood flow in the retinal veins gradually drops. Consequently, venous congestion and expansion of the capillaries lead to a rapid drop in blood flow. There is a destruction of the "blood-retina" barrier, causing hypoxia of retinal fibers. As the pathogenesis progresses, conditions are created for fluid extravasation from the capillaries into the peripapillary retina and the optic disc, the state of the optic nerve being further aggravated by its mechanical compression at the orbital apex by EOM caused by increase in their volume.

Diagnosis of ON in patients with edematous exophthalmos is not easy and remains unclear [2, 38, 39]. Table 1 displays the defining symptoms of ON from literature.

From Table 1, it is difficult to establish an afferent pupillary defect, as the process is usually bilateral. Permanent visual impairment, dyschromatopsia, visual field defects, and edema of the optic disc are the signs that indicate the beginning of the visual destruction. There is an opinion that the diagnosis of ON should be based on at least two of the signs (impairment of visual acuity, color blindness, optic disc edema and/or signs of ON detected by MRI [presence of "apical congestion" and/or stretching of the optic nerve]) [41], though these are all symptoms of advanced ON. According to several reports, the diagnosis of ON remains complicated due to the lack of clearly defined criteria [2, 38, 39]. Several publications claim that MRI-detected changes in the optic nerve correlate with clinical signs of the disease process (sub- and decompensation), and this suggests the possibility of using MRI in its diagnosis [42–44]. It should be noted that these are all late

Symptoms and signs of optic neuropathy in patients with edematous exophthalmos
Симптомы и признаки оптической нейропатии у пациентов с отёчным экзофтальмом

Early symptoms and signs of optic neuropathy	Symptom frequency	References
Decreased visual acuity, color vision impairment	> cases	[2]
Afferent pupil defect, impaired visual acuity, visual field defects, dyschromatopsia	Determining the diagnosis	[3]
Permanent visual impairment	> cases	[4]
Blurring or "desaturation" of color, or appearance of relative scotomata with normal visual acuity	> cases	[5]
Visual impairment	83%	[6]
Impaired visual acuity Visual field defects Optic disc edema Color impairment	85% 80% 42% 100%	[40]
Clearly defined criteria for optic neuropathy	None	[2, 38, 39]

signs of ON. In addition, we should note that in half of EOP cases (with and without ON), CT and MRI studies do not reveal significant differences in the mean volumes of the musculi recti [14, 16].

Clinical aspects of initial ON: The clinical presentation of ON was studied in 68 out of 103 edematous exophthalmos patients. In all cases, the process was bilateral. The disease started gradually in the presence of subcompensated or decompensated edematous exophthalmos (Fig. 1).

Visual impairment did not depend on the time of the day. The gradual development of clinical symptoms is represented as follows. Initially, the dilated retinal veins are visualized ophthalmoscopically at an early stage of ON development, when the difficulty in venous outflow through the superior orbital fissure occurs (Fig. 2, *a*).

Simultaneously or earlier, in the visual field, 1–3 small relative or absolute scotomata located paracentrally can be detected. A minor impairment of central vision is also possible (by 1–2 lines). This marks the development of venous insufficiency, which also affects the tissues of the eye, leading to a disorder of microcirculation in the retina and hypoxia of its ganglion cells. This causes scotomata with normal visual acuity and the absence of pronounced changes in the fundus [7, 21, 33, 34]. Deterioration of vision progresses for several days. Subsequently, the optic disc becomes hyperemic, and initial signs of its partial edema are possible (Fig. 2, *b*). The process during this period is reversible [7, 45]. The presence of any of the three aforementioned signs in patients with sub- or decompensated edematous exophthalmos indicates initial ON: dilatation of retinal veins with normal vision, presence of relative scotomata with normal visual acuity, minor impairment of visual acuity (by 1–2 lines), and advanced impairment of visual acuity, hyperemia, papilledema (advanced stage of ON).

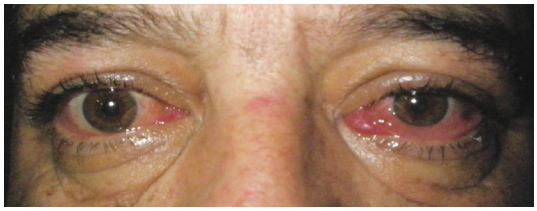
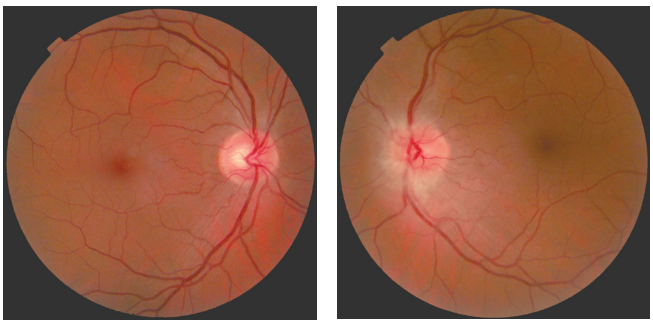


Fig. 1. Patient K., 49 years old. Clinical diagnosis: RE – subcompensated edematous proptosis; LE – decompensated edematous proptosis

Рис. 1. Пациент К., 49 лет. Клинический диагноз: OD — субкомпенсированный отёчный экзофтальм; OS — декомпенсированный отёчный экзофтальм



a *b*

Fig. 2. The same patient's K. fundus photo: *a* – RE, initial optic neuropathy in subcompensated edematous proptosis; *b* – LE, developed optic neuropathy in decompensated edematous proptosis

Рис. 2. Фото глазного дна того же пациента К.: *a* — OD, начальная оптическая нейропатия на фоне субкомпенсированного отёчного экзофтальма; *b* — OS, развитая оптическая нейропатия на фоне декомпенсированного отёчного экзофтальма

CONCLUSION

Since the early XXI century, specialists dealing with the EOP problem are concerned with the question whether ON is a clinical diagnosis or a determinable phenomenon [46]. The proposed concept of the primacy of venous insufficiency in its pathogenesis in EOP patients answers this query. ON is a complication of an advanced disease which treatment should be aimed primarily at improving venous outflow through active dehydration and non-specific anti-inflammatory therapy. Interventions such as decompression surgeries are indicated only in the absence of a response to drug therapy.

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