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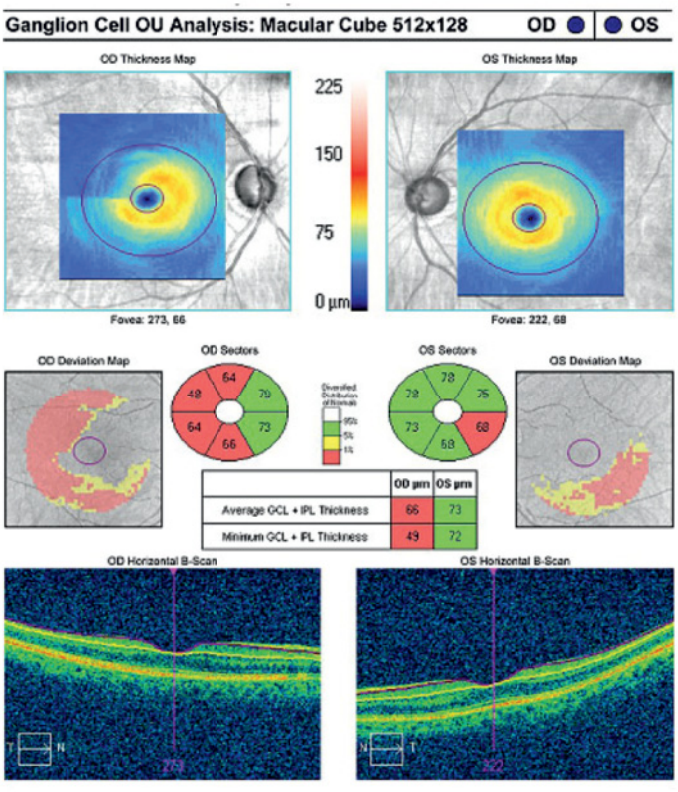

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Фондация „Национална Академия Глаукома"

Уважаеми колеги,

Имаме честта да Ви поканим на **XV Юбилеен Международен Симпозиум на Фондация „Национална Академия Глаукома"**, който ще се състои в **гр. София на 18 Април 2026 г. в Хотел „Форум"**.

В рамките на симпозиума ще се проведе и **сесия „Ретина"**.

При желание от Ваша страна да изнесете доклад в рамките на симпозиума, моля да изпратите заглавие, автори и институция на български и английски език до 1-ви март 2026 г. на електронната поща на фондацията.

За контакти, регистрация и информация: **E-mail: botio.anguelov@abv.bg**

Проф. д-р Ботьо Ангелов д.м.
Учредител и Управител на Фондация „Национална Академия Глаукома"

Objective methods of evaluation of retinal ganglion cell function in clinical settings: a structured literature review

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Abstract

Retinal ganglion cells (RGCs) are the retina's sole output neurons, transmitting visual information from the eye to the brain. Their degeneration underlies vision loss in numerous ocular and systemic diseases, most notably glaucoma. However, traditional subjective visual tests, such as standard automated perimetry (SAP), often fail to detect early RGC dysfunction, with substantial neuronal loss occurring before measurable visual field defects. This highlights the urgent need for objective, sensitive methods to detect, monitor, and guide treatment for RGC-related diseases.

This review presents a comprehensive analysis of objective clinical methods for assessing RGC function and structure. Functional evaluation tools include the Pattern Electroretinogram (PERG), Visual Evoked Potential (VEP), and Photopic Negative Response (PhNR), each offering unique advantages for detecting early and potentially reversible RGC dysfunction. Structural techniques - primarily optical coherence tomography (OCT) and OCT angiography (OCTA) - provide high-resolution imaging of RGC axons, somas, and associated microvasculature. Together, these approaches offer complementary insights: while OCT quantifies established structural loss, PERG and PhNR can detect dysfunction before irreversible damage, providing a therapeutic window for neuroprotective strategies.

Despite progress, challenges persist. These include the structure-function discrepancy, RGC subtype heterogeneity, poor standardization of electrophysiological protocols, limitations in image quality and reproducibility of OCTA, and insufficient adoption of promising tools like PERG due to limited large-scale clinical validation. Furthermore, a deeper understanding is needed of the transition from RGC dysfunction to death, particularly to refine treatment timing.

The distinction between functional and structural measures is not competitive but complementary. An integrative, multimodal assessment strategy - combining electrophysiological and imaging modalities - holds the greatest promise for early diagnosis, risk stratification, treatment monitoring, and the development of novel neuroprotective and regenerative therapies. Bridging existing gaps will require technological refinement, translational research, and widespread clinical standardization.

Key words: Retinal Ganglion Cells (RGCs), Objective Functional Assessment, Photopic Negative Response (PhNR), Optical Coherence Tomography (OCT), Multimodal Diagnostic Strategies.

I. Introduction

A. The Critical Role of Retinal Ganglion Cells (RGCs) in Vision and Disease

Retinal ganglion cells (RGCs) serve as the exclusive output neurons of the retina, holding the fundamental responsibility for transmitting visual stimuli from the eye to the brain [1]. Their axons coalesce to form the optic nerve, a crucial conduit that relays visual information to higher brain centers, notably the lateral geniculate nucleus (LGN). Beyond their role in mere signal propagation, RGCs are actively engaged in the initial stages of visual information processing, enabling the discernment of intricate visual attributes such as spatial contrast, flicker, color, fine details, motion, and absolute light levels [2, 3].

The structural and functional integrity of RGCs is indispensable for the maintenance of normal visual acuity and perception. Consequently, any compromise to these cells, whether through dysfunction or irreversible loss, constitutes the primary determinant of visual impairment across a broad spectrum of traumatic and degenerative ocular conditions.

B. Rationale for Objective Assessment of RGC Function in Clinical Practice

Numerous ophthalmic and systemic pathologies are characterized by the degeneration of RGCs. Glaucoma, for instance, stands as a leading global cause of irreversible blindness, fundamentally defined by the progressive degeneration and apoptosis of RGCs and their axons [4]. This RGC loss, akin to damage in other parts of the central nervous system, is largely irreversible. Other significant conditions impacting RGCs include various optic neuropathies, such as optic neuritis (frequently observed in multiple sclerosis), ischemic optic neuropathy, compressive optic neuropathy, and toxic optic neuropathies [5]. Furthermore, emerging evidence has linked RGC health to systemic conditions, with recent studies documenting a measurable reduction in ganglion cell layer thickness in individuals who have recovered from coronavirus disease 2019 (COVID-19), suggesting a potential neurodegenerative effect on the optic nerve [6].

A significant challenge in managing these conditions is the inherent limitation of traditional subjective visual function tests. Standard automated perimetry (SAP), a cornerstone of glaucoma diagnosis, often fails to detect RGC damage until the disease is considerably advanced. Estimates suggest that a substantial proportion of RGCs, ranging from 20% to 50%, may be lost before statistically significant abnormalities manifest in visual field testing [7]. This phenomenon, often termed "silent progression", means that by the time patients experience noticeable visual field deficits and receive a diagnosis through conventional methods, the disease has progressed to a

moderate stage, potentially beyond the optimal window for neuroprotective interventions aimed at preserving distressed but still viable cells. This fundamental limitation of subjective tests underscores the critical need for objective methods of RGC assessment [4].

The imperative for accurate and reliable objective assessment of RGC numbers and function extends beyond early diagnosis to the development and evaluation of novel therapeutic strategies. In particular, the efficacy of neuroprotective and regenerative approaches, which aim to halt or reverse RGC damage, can only be robustly determined through quantitative, patient-independent measures. Objective methods thus provide essential tools for early detection, precise monitoring of disease progression, and rigorous evaluation of treatment outcomes.

This literature review provides a comprehensive, structured analysis of objective methods currently utilized or under active development for evaluating RGC function in clinical settings.

II. Retinal Ganglion Cell Biology and Pathophysiology

A. Fundamental Anatomy and Physiology of RGCs

Retinal ganglion cells are positioned as the ultimate neuronal relays within the retinal circuitry, receiving complex visual inputs from photoreceptors via an intricate network of intermediate bipolar and amacrine cells. Their axons converge at the optic disc, forming the optic nerve, which subsequently transmits these meticulously processed visual signals to various higher brain centers, with the lateral geniculate nucleus (LGN) being a primary projection target. The human retina is home to approximately 1.2 million RGCs. Crucially, these cells do not represent a homogeneous population; rather, they comprise up to 30 distinct subtypes, each categorized by unique morphological, functional, genetic, and immunohistochemically characteristics [2].

During early development, RGCs undergo a conserved neurogenic program, emerging as one of the first neuronal cell types generated within the retina. In mammalian models, RGCs are born between embryonic day 11 and post-natal day zero in mice, and in humans, this process occurs between week 5 and week 18 of gestation. Their development progresses in a wave-like pattern across the retina, guided by a complex interplay of signaling factors and transcription networks [8].

B. Intrinsic Challenges in RGC Assessment: Subtype Heterogeneity and the Interplay of Dysfunction and Death

The objective assessment of RGC health is complicated by several intrinsic factors.

Subtype Heterogeneity: The remarkable diversity of RGC subtypes, with up to 30 distinct types, presents a substantial challenge for comprehensive evaluation. These subtypes exhibit differential responses to disease and treatment, and current objective evaluation techniques may selectively identify or inadvertently overlook particular subpopulations. This selective sensitivity limits the comprehensive appropriateness of these measures for assessing overall RGC survival and function. For example, some RGC subtypes have demonstrated greater resilience to optic nerve damage or ocular hypertension compared to others, indicating varied vulnerability profiles [3]. The implication of this cellular diversity is that a single objective method might not be equally sensitive to all RGC populations, potentially leading to an incomplete or even misleading assessment of overall RGC health.

Dysfunction vs. Death: A critical aspect of RGC pathology is that cellular dysfunction often precedes irreversible cell death. The precise relationship between RGC death and dysfunction, and the comparative accuracy and reliability of various techniques in distinguishing between these two states, remain areas requiring deeper understanding. The observation that RGCs can be dysfunctional before they undergo irreversible cell death implies that the primary objective of early detection is not merely to identify irreversible damage but, more importantly, to identify reversible dysfunction. This opens a crucial therapeutic window for neuroprotective strategies aimed at rescuing these "distressed but still viable cells" [9].

Functional objective tests, such as Pattern Electroretinogram (PERG) and Photopic Negative Response (PhNR), become particularly valuable in this context as they can detect these subtle, potentially reversible changes before structural loss becomes evident. The evolving paradigm of RGC assessment is thus shifting from simply diagnosing established damage to identifying a "functional tipping point", thereby guiding early, targeted interventions to preserve vision rather than merely managing irreversible loss [10].

"Silent Progression": A major clinical hurdle is the phenomenon of "silent progression", where significant RGC damage can occur before traditional subjective tests, such as standard automated perimetry, detect a functional loss. Estimates indicate that between 20% and 50% of RGCs may be lost before statistical abnormalities become apparent in visual field testing. This substantial delay in detection means that by the time a patient experiences noticeable visual field loss and receives a diagnosis via traditional methods, the disease is already moderately advanced, potentially past the optimal window for neuroprotective interventions [7].

III. Evolution and Current Landscape of Objective RGC Function Evaluation Methods

The landscape of objective RGC function evaluation has undergone a significant evolution, driven by the need for more sensitive and specific diagnostic and monitoring tools. This progression reflects a continuous drive towards higher resolution and more precise localization of RGC pathology.

A. Electrophysiological Techniques

Electrophysiological tests offer objective and quantitative measures of retinal and visual pathway function through the recording of electrical signals generated in response to controlled visual stimuli. These methods are indispensable for assessing RGC function, serving as a crucial complement to structural evaluations.

1. Pattern Electroretinogram (PERG)

a. Principles, Historical Development, and Seminal Studies

The Pattern Electroretinogram (PERG) is a non-invasive electrophysiological test that provides an objective and quantitative measurement of central retinal function, primarily

reflecting the electrical activity of RGCs. It is elicited by contrast-reversing patterned stimuli, such as sinusoidal gratings or checkerboards, presented at a constant mean luminance [10]. The PERG waveform typically comprises two main components: a positive peak (P50) and a larger negative trough (N95). While the P50 component receives contributions from both outer and inner retinal neurons, the N95 component is primarily generated by the spiking activity of RGCs and demonstrates high sensitivity to retinal nerve fiber degeneration and RGC loss [11].

Various investigations consistently confirmed PERG alterations in conditions such as glaucoma and ocular hypertension [8]. To ensure consistency and comparability across laboratories worldwide, the International Society for Clinical Electrophysiology of Vision (ISCEV) has since developed and published standardized guidelines for PERG recordings [11].

b. Clinical Applications and Diagnostic Utility

Studies have consistently shown that PERG amplitude loss correlates with the progressive loss of RGCs and optic nerve fibers, and importantly, PERG changes can even anticipate structural loss in early manifest glaucoma. A reduced PERG amplitude has been demonstrated to predict subsequent conversion to glaucomatous visual field defects and an increased rate of progressive retinal nerve fiber layer thinning in suspect eyes, highlighting its potential utility in risk stratification. Furthermore, the assessment of PERG spatial tuning can provide an early, though not entirely specific, indicator of RGC dysfunction in diseases such as early glaucoma and multiple sclerosis. In clinical practice, PERG is often employed as a follow-up test when an abnormal pattern VEP is observed, helping to differentiate whether the abnormality originates from retinal or optic nerve dysfunction, thereby providing crucial localization information [10, 12].

2. Visual Evoked Potential (VEP)

a. Principles, Historical Development, and Seminal Studies

Visual Evoked Potentials (VEPs) are electrophysiological signals that represent the aggregate electrical activity of the entire visual pathway, extending from the optic nerve to the calcarine cortex [25]. VEPs are typically recorded from electrodes strategically placed on the occipital scalp. The most common stimulus types employed are pattern reversal (PR-VEP), where light and dark elements (e.g., checkerboard or bars) reverse contrast while maintaining a constant mean luminance. The PR-VEP waveform is characteristically triphasic, featuring an initial negativity (N75), a prominent positive peak (P100) occurring around 100 ms, and a subsequent negativity (N135). The P100 component is particularly stable and repeatable, widely recognized as the electrical correlate of primary visual cortex activity [13].

The VEP practical clinical application became feasible only with the advent of signal-averaging computers in the early 1960s. These computers enabled the extraction of the time-locked VEP signal from background electroencephalographic (EEG) noise by repeatedly presenting stimuli and averaging the corresponding responses. Pattern reversal VEPs subsequently became the preferred clinical technique [14]. To standardize clinical VEP recordings and ensure consistency, ISCEV has developed and regularly updates international guidelines [13].

b. Clinical Applications and Diagnostic Utility

VEPs are extensively utilized in neuro-ophthalmology for the quantification and monitoring of functional damage across a broad spectrum of optic neuropathies. This includes inflammatory conditions such as optic neuritis (often associated with multiple sclerosis), ischemic optic neuropathy (e.g., NAION), and compressive optic neuropathies, as well as traumatic, hereditary, degenerative, and toxic-metabolic etiologies. They are particularly effective in detecting demyelination, which characteristically manifests as delayed VEP responses due to impaired neural signal transmission [15, 16].

VEPs also serve as an objective method for assessing visual acuity in patient populations unable to provide reliable subjective responses, such as non-verbal infants, individuals with low intellectual abilities, or those suspected of malingering. In cases of optic nerve compression, for example, due to pituitary tumors, VEPs can reveal characteristic abnormalities, including latency delays and a “crossed” VEP asymmetry indicative of chiasmal dysfunction, and may even serve as a prognostic indicator for visual outcome following surgical decompression [15, 17].

It is important to recognize that VEPs reflect the functional integrity of the entire visual pathway from the retina to the striate cortex and possess a significant macular contribution. Consequently, VEP abnormalities are highly non-specific; they can be influenced by any pathology upstream in the visual pathway.

3. Photopic Negative Response (PhNR)

a. Principles, Historical Development, and Seminal Studies

The Photopic Negative Response (PhNR) is a slow, negative-going component of the cone-driven full-field electroretinogram (ERG) that appears after the b-wave. It is profoundly dependent on the integrity of retinal ganglion cell responses and reflects the functional status of the inner retinal layers. While its primary origin is the electrical activity of RGCs themselves, its relatively slow timing suggests mediation and contribution from amacrine and glial cells [18, 19, 20].

Unlike the PERG, the PhNR is elicited by a uniform full-field stimulus, which confers an advantage in clinical settings by making it less critically dependent on accurate refraction, clear ocular media, or precise fixation control. A unique benefit of the PhNR is its ability to enable simultaneous assessment of distal retinal function (i.e., cone photoreceptor and bipolar cell responses) from the same recording. To standardize the technique and optimize clinical applications, the ISCEV has since provided an extended protocol for recording and analyzing the PhNR [20, 21].

b. Clinical Applications and Diagnostic Utility

The PhNR provides an objective measure of retinal ganglion cell function and demonstrates particular sensitivity to glaucomatous damage. It has proven to be an effective objective clinical diagnostic test for assessing RGC function in various optic neuropathies [22]. A significant advantage of the PhNR is its capacity to reflect reversible aspects of RGC dysfunction. Studies have shown that improvements in PhNR amplitude can

occur within 1-2 months following intraocular pressure (IOP) lowering, with a direct correlation to the degree of IOP reduction. This characteristic suggests its utility in monitoring the efficacy of glaucoma treatments [23].

A markedly reduced PhNR, particularly when focal or multifocal for the central 15 degrees, is indicative of RGC dysfunction in early stages of glaucoma (including suspects) and can aid in stratifying the risk for disease progression [24, 25, 26]. Compared to PERG, the PhNR captures a more global RGC response, can be recorded using skin electrodes (which are better tolerated by pediatric patients), and does not necessitate prolonged or strict fixation, making it more feasible for certain patient populations. It is also valuable in detecting RGC dysfunction that predominantly affects the peripheral retina [27, 28].

B. Structural Imaging Techniques

Structural imaging techniques provide quantitative assessments of RGCs and their axons by precisely measuring the thickness and morphology of specific retinal layers. As they are correlated, but not directly representing retinal function, they will be discussed less extensively in this work.

1. Optical Coherence Tomography (OCT)

a. Assessment of Retinal Nerve Fiber Layer (RNFL) and Ganglion Cell Complex (GCC/GC-IPL) Thickness

OCT provides precise and reproducible measurements of the thickness of the retinal nerve fiber layer (RNFL), which is composed of RGC axons, and the ganglion cell layer (GCL). With continuous advancements in segmentation algorithms, OCT can also quantify the ganglion cell-inner plexiform layer (GC-IPL) thickness or the broader ganglion cell complex (GCC), which typically includes the RNFL, GCL, and inner plexiform layer (IPL) [29, 30]. By analyzing the thickness and morphology of these innermost retinal layers, clinicians can objectively infer the health and integrity of RGCs. The macula, with its exceptionally high density of RGCs, represents a critical region for assessment, and macular thickness measurements, particularly of the GCC, serve as a valuable surrogate indicator of RGC damage [31].

b. Clinical Applications and Diagnostic Utility

OCT has become the most widely used technique for ganglion cell analysis in neuro-ophthalmology. It is broadly considered the gold standard for objectively evaluating structural changes in the optic nerve head and inner retinal layers affected by diseases such as glaucoma [32]. A key advantage of OCT is its ability to facilitate early detection and monitoring of various neuro-ophthalmological conditions, including glaucoma, optic neuritis, multiple sclerosis (MS), ischemic optic neuropathy, and compressive optic neuropathy [33]. The average GCC thickness and its related parameters are considered reliable biomarkers for detecting preperimetric glaucomatous damage and can correlate with progressive visual field loss.

2. Optical Coherence Tomography Angiography (OCTA)

a. Assessment of RGC Microvasculature and Perfusion

OCTA allows for a layer-specific assessment of the intricate microcirculatory network that supplies the RGCs. This includes detailed visualization of the superficial capillary plexus (SCP), the deep capillary plexus (DCP) of the macula, and the radial peripapillary capillary plexus (RPCP) surrounding the optic disc. The technology directly visualizes vascular changes associated with RGC damage [34]. Vascular deterioration assessed by OCTA has been shown to correlate closely with structural and functional damage in glaucoma, with changes in retinal microcirculation potentially preceding structural abnormalities in the optic nerve head. This highlights that impaired ocular blood flow or microvascular dysregulation may be an early indicator or a contributing factor to RGC dysfunction and degeneration, particularly in conditions like glaucoma where intraocular pressure-independent mechanisms are increasingly recognized [35]. This makes OCTA a novel, non-IOP-related biomarker for RGC health, potentially leading to new diagnostic criteria and therapeutic targets focused on improving ocular perfusion and metabolic support for RGCs.

b. Clinical Applications and Diagnostic Utility

OCTA is increasingly integrated into glaucoma management to assess changes in the optic nerve head microvasculature and the peripapillary capillary network [36]. Its ability to visualize these microvascular changes at an early stage, even before visual field defects become detectable, positions it as a valuable tool for early diagnosis, particularly in normotensive glaucoma where structural changes might be subtle. OCTA also plays a role in monitoring disease progression by tracking changes in the perfusion of the retinal nerve fiber layer and the ganglion cell complex [34]. It provides complementary information to visual field and structural OCT examinations, contributing to a more comprehensive glaucoma diagnosis, progression detection, and risk assessment.

The distinction between electrophysiological methods (PERG, VEP, PhNR) that assess RGC function and imaging methods (OCT, OCTA) that assess RGC structure and microvasculature is not a competitive one, but rather a complementary relationship. The fact that functional changes, such as PERG alterations, can precede histological RGC loss, and that PhNR can reflect reversible dysfunction, highlights that functional tests offer a critical window for intervention before irreversible structural damage occurs. This means that while structural tests quantify established loss, functional tests can identify early dysfunction, providing an opportunity for timely therapeutic intervention.

IV. Conflicting Viewpoints and Limitations of Current Objective Methods

Despite significant advancements, objective methods for RGC function evaluation are not without their limitations and areas of ongoing debate. These challenges often stem from the complex biology of RGCs and the inherent difficulties in translating high-resolution research tools into routine clinical practice.

A. General Challenges in RGC Assessment: The Structure-Function Discrepancy and Subtype Specificity

A persistent challenge across all objective methods is the precise understanding of the relationship between RGC dysfunction and irreversible cell death, as well as the comparable accuracy and reliability of various techniques in discerning these distinct states [37]. While it is known that

Table 1. Comparison of Key Objective RGC Evaluation Methods.

Method	Primary RGC Aspect Assessed	Underlying Principle (brief)	Main Clinical Applications	Key Advantages	Key Disadvantages
Pattern Electroretinogram (PERG)	Functional (electrical activity, particularly spiking activity of RGCs)	Electrical response to patterned stimuli with constant mean luminance, isolating RGC activity	Glaucoma diagnosis/ monitoring, Optic Neuropathies (e.g., optic neuritis, compressive)	Objective, Non-invasive, Early detection of dysfunction, Can anticipate structural loss	Small signals, Requires patient cooperation/ fixation, Often corneal electrodes, Sensitive to refractive error, Limited topographical info
Visual Evoked Potential (VEP)	Functional (electrical activity of entire visual pathway from retina to cortex)	Electrical response of cortical neurons to visual stimuli, recorded from scalp electrodes	Optic Neuropathies (inflammatory, demyelinating, compressive, etc), Objective visual acuity assessment	Objective, Non-invasive, Assesses entire visual pathway, Useful for non-verbal patients	Highly non-specific (affected by any upstream pathology), Lack of RGC-specific assessment
Photopic Negative Response (PhNR)	Functional (electrical activity of inner retina, primarily RGCs and their axons)	Slow negative component of full-field ERG, elicited by uniform flash, reflecting RGC function	Glaucoma diagnosis/ monitoring, Optic Neuropathies, Monitoring treatment efficacy (reversible dysfunction)	Objective, Non-invasive, Less dependent on clear media/ refraction/fixation than PERG, Can reflect reversible dysfunction, Global RGC response	Less consensus on optimal protocol, Requires pupil dilation, Lacks detailed topographical info, Potential false negatives in early glaucoma
Optical Coherence Tomography (OCT)	Structural (thickness and morphology of RNFL, GCL, IPL/ GCC)	Low-coherence interferometry to generate cross-sectional images of retinal layers	Glaucoma diagnosis/ monitoring, Optic Neuropathies (optic neuritis, MS, ischemic, compressive)	Objective, Non-invasive, High resolution, Early detection of structural damage, Quantitative measurement	"Floor effect" in advanced disease, segmentation errors, Over-reliance on summary statistics
Optical Coherence Tomography Angiography (OCTA)	Microvascular (perfusion, vessel density, vascular changes associated with RGC damage)	Motion contrast (decorrelation signal from moving red blood cells) to map blood flow	Glaucoma diagnosis/ monitoring (especially early/ normotensive), Assessing vascular changes in RGC damage	Non-invasive, Dye-free, Visualizes microvasculature, Can detect changes preceding structural abnormalities	Susceptible to motion artifacts, Poor image quality often reported, Media opacities/pupil size affect quality, Projection artifacts obscure deep layers,

dysfunction often precedes death, quantifying this transition objectively remains complex.

The inherent heterogeneity of RGC subtypes, with up to 30 distinct types, significantly complicates the measurement process. Current techniques may selectively identify or inadvertently overlook particular subpopulations, thereby limiting their comprehensive appropriateness and potentially leading to an incomplete picture of disease progression. Different RGC subtypes demonstrate varying resilience or susceptibility to optic nerve damage, ocular hypertension, or photoreceptor degeneration, further complicating a uniform assessment [38, 39].

B. Limitations and Controversies in Electrophysiological Methods (PERG, VEP, PhNR)

1. Pattern Electroretinogram (PERG)

While widely accepted as an RGC-sensitive test, the precise cellular origin of the PERG, particularly the relative contributions from spiking versus non-spiking activity and the potential involvement of non-RGC neurons (e.g., glial cells, more distal neurons), remains a subject of some contention [10]. Some sources argue that PERG alone may not be a sufficiently specific assay of RGC function, as its generation can depend on intact outer retinal signals [40].

From a practical standpoint, PERG signals are relatively small, necessitating precise recording conditions and often the use of corneal electrodes. These electrodes may not be well-tolerated by all patients, particularly children. Optimal refractive correction is also crucial to prevent degradation of the retinal image contrast, which can impact signal quality [41]. The diagnostic accuracy of PERG can vary, with some studies finding it to perform no better than, or even worse than, standard automated perimetry (SAP) or other perimetric tests in discriminating between healthy and glaucomatous eyes [42]. As PERG primarily assesses macular RGC function, it may be insensitive to peripheral visual field constriction that can occur in some conditions.

A notable ongoing controversy is that some medical policies continue to classify PERG as "experimental/investigational" for all indications, citing perceived insufficient scientific evidence

compared to established alternatives [43]. This classification points to a significant translational gap. Despite promising research findings on PERG's utility in early detection and predicting progression, the lack of widespread acceptance by some regulatory bodies underscores a critical need for larger, longer-duration, multi-center studies to provide the robust evidence required for universal clinical adoption and reimbursement.

2. Visual Evoked Potential (VEP)

The primary limitation of VEPs lies in their non-specificity. VEPs reflect the electrical activity of the entire visual pathway, from the retina to the striate cortex [44]. Consequently, VEP abnormalities are highly non-specific; they can be influenced by any pathology upstream in the visual pathway, including macular dysfunction, and are not solely indicative of primary optic nerve or RGC disease. This inherent lack of specificity necessitates complementary tests, such as PERG, to precisely localize the site of dysfunction within the visual pathway [45]. Therefore, the interpretation of VEPs should rarely be used in isolation to avoid potential misdiagnosis.

3. Photopic Negative Response (PhNR)

While promising for detecting early RGC impairment, distinguishing between healthy subjects and individuals at risk of developing glaucomatous damage remains challenging for PhNR. Some studies have reported normal PhNR responses even in patients with confirmed glaucomatous defects detected by other methods (e.g., visual field, multifocal VEP, SD-OCT), suggesting the potential for false negatives [20, 27].

As a relatively newer technique compared to PERG, there is less consensus on the optimal protocol for PhNR, including specific stimulus characteristics (intensity, chromaticity) and signal analysis methods [21]. Some stimulus conditions may be more difficult to record than others [46]. While recording reliability and diagnostic efficacy are generally improved by pupil dilation, this can be a practical disadvantage in routine clinical settings. Similar to PERG, the PhNR lacks detailed topographical information compared to multifocal electrophysiological tests. While it reflects global RGC activity, current OCT technology might not fully capture corresponding peripheral RGC changes, potentially leading to a poor structure-function correlation in some conditions.

C. Limitations and Challenges in Structural Imaging Methods (OCT, OCTA)

1. Optical Coherence Tomography (OCT) - RNFL/GCC/GC-IPL

While excellent for early detection, OCT measurements of retinal layer thickness can exhibit a "floor effect" in more advanced stages of neurodegenerative diseases. This means that once a certain amount of RGC loss has occurred, further thinning may not be reliably detected, thereby limiting its utility for monitoring progression in severe disease [47]. Segmentation errors by automated algorithms are a common issue, particularly in the presence of epiretinal membranes, vitreous detachments, or poor image contrast, which can lead to inaccurate thickness measurements. Over-reliance on computer-driven summary statistics without careful visual scrutiny of the actual scan images can lead to discrepancies with visual field results and miss subtle, localized damage, especially within the macula. OCT can also yield "false positives", sometimes termed "red disease", due to anatomical variations that mimic glaucomatous thinning [48, 49].

The limitations of OCT are not solely technical (e.g., segmentation errors, motion artifacts). A critical, often overlooked, challenge lies in the human element: the failure of clinicians to visually scrutinize high-quality images and an over-reliance on automated summary statistics [50]. This suggests that technological advancements alone are insufficient; improved clinician training and standardized interpretation guidelines are equally crucial for maximizing diagnostic accuracy and avoiding misdiagnosis. Even with high-resolution images, if clinicians do not properly inspect them or over-rely on potentially flawed algorithms, diagnostic accuracy is compromised. This means that future improvements in RGC imaging require a multi-pronged approach: continued technological refinement combined with enhanced education, standardized image analysis protocols, and potentially AI-driven tools to assist in interpretation, thereby bridging the gap between data acquisition and meaningful clinical insight.

2. Optical Coherence Tomography Angiography (OCTA)

OCTA is highly susceptible to motion artifacts due to its relatively prolonged acquisition times, which can manifest as vertical bands or duplication of vessels on the angiography map. A high number of poor-quality images have been reported in studies, which can compromise diagnostic reliability [51]. Media opacities, such as vitreous opacities, and inadequate pupillary dilation can significantly degrade scan quality and the accurate quantification of vessel densities. Current OCTA technology primarily visualizes superficial retinal vessels effectively but struggles with deeper retinal and choroidal vasculature due to projection artifacts, which can obscure true deep-layer microvascular dropout [52]. OCTA measurements generally exhibit lower reproducibility compared to structural OCT measurements, which is an important consideration for monitoring disease progression. Furthermore, measurements obtained from different commercially available OCTA algorithms vary significantly, limiting their interchangeability and comparability across platforms [53]. Similar to OCT, vessel density reduction on OCTA can reach a "floor" at more advanced disease stages, potentially limiting its ability to monitor progression in very severe cases. OCTA parameters are also influenced by various factors, including disease severity, subject demographics (age, ethnicity), diurnal changes, exercise, and systemic conditions (e.g., hypertension, diabetes), adding to measurement variability [53]. As a relatively new technology, there is currently a lack of long-term longitudinal studies evaluating OCTA's ability to detect progression over extended periods.

V. Gaps in Current Literature and Unmet Needs

Despite the remarkable progress in objective RGC evaluation, several critical gaps and unmet needs persist within the current literature and clinical practice. Addressing these areas is crucial for further advancing the diagnosis, monitoring, and treatment of RGC-related pathologies.

A. Elucidating the Relationship Between RGC Dysfunction and Irreversible Cell Death

The precise relationship between RGC dysfunction and irreversible cell death remains poorly understood. While it is recognized that cellular dysfunction often precedes irreversible cell death, the exact mechanisms and temporal dynamics of this transition are not fully elucidated. Current objective methods, while sensitive, do not always clearly differentiate between a cell that is merely dysfunctional (and potentially salvageable) and one that is irreversibly destined for apoptosis. A deeper understanding of this continuum is essential for identifying the optimal therapeutic window for neuroprotective strategies.

B. Overcoming Subtype Specificity and Heterogeneity in Assessment

The existence of up to 30 distinct RGC subtypes, each with unique functional properties and differential vulnerability to disease and treatment, presents a significant challenge [1]. Current evaluation techniques may selectively identify or inadvertently overlook particular subpopulations, thereby limiting their comprehensive appropriateness as measures of overall RGC survival and function [1]. There is a pressing need for methods that can broadly capture all RGC populations or, ideally, tools that can specifically differentiate and quantify dysfunction within vulnerable subtypes. This would allow for a more nuanced understanding of disease pathogenesis and targeted therapeutic interventions.

C. Enhancing the Clinical Utility and Accessibility of Advanced Imaging

While Adaptive Optics (AO) offers unprecedented cellular-level resolution for RGC imaging [53], its current limitations in clinical settings are substantial. These include high cost, technical complexity, long acquisition times, inconsistent image quality, and the lack of a standardized database for interpretation [53]. The current restriction of most AO devices to research use highlights a significant gap in translating cutting-edge technology into widespread clinical benefit. There is a critical unmet need for more user-friendly, cost-effective, and faster AO systems that can seamlessly integrate into routine clinical workflows.

D. Improving the Diagnostic Accuracy and Reproducibility of OCTA

Optical Coherence Tomography Angiography (OCTA), while a promising tool for assessing RGC microvasculature, faces limitations in image quality, susceptibility to artifacts (e.g., motion, projection), and lower reproducibility compared to conventional OCT [49]. The variability in measurements across different commercial algorithms also limits their interchangeability. Addressing these technical challenges is crucial to enhance OCTA's reliability and consistency in detecting early vascular changes and monitoring disease progression. There is also a need for long-term longitudinal studies to fully validate its predictive capabilities.

E. Bridging the Translational Gap for Promising Electrophysiological Methods

The classification of some promising objective methods, such as PERG, as "experimental/investigational" by certain medical policies [58], despite evidence of their utility in early detection and predicting progression, highlights a significant translational gap. This is not merely a bureaucratic hurdle but reflects a critical need for larger, longer-duration, multi-center studies to provide the robust evidence required for widespread clinical adoption and reimbursement.

VI. Suggestions for Future Research

Future research in objective RGC function evaluation should focus on several key areas to address the identified gaps and limitations, ultimately leading to more effective clinical management of RGC-related diseases.

Developing Multimodal and Integrated Assessment Platforms. Future efforts should prioritize the development of integrated multimodal platforms that combine the strengths of various objective methods. This would involve fusing functional electrophysiological data (PERG, PhNR) with high-resolution structural (OCT, AO-OCT) and microvascular (OCTA) imaging.

Investigating RGC Subtype-Specific Biomarkers. Given the significant heterogeneity of RGCs, future research must aim to identify and validate objective biomarkers that are specific to individual RGC subtypes. This could involve refining existing electrophysiological and imaging techniques to selectively probe or visualize particular RGC populations, or developing novel methods that leverage genetic or molecular markers. Understanding how different RGC subtypes respond to disease and treatment will enable more precise diagnostic criteria and the development of highly targeted therapies.

Longitudinal Studies and Normative Databases. There is a critical need for large-scale, long-term longitudinal studies to track RGC function and structure in diverse patient populations. Such studies are vital for establishing robust normative databases across different age groups and ethnicities, which are currently lacking for many advanced techniques. Longitudinal data will also be crucial for validating the predictive value of emerging biomarkers, understanding the natural history of RGC degeneration, and assessing the long-term efficacy of new treatments.

Artificial Intelligence and Machine Learning Integration. The integration of artificial intelligence (AI) and machine learning algorithms holds immense promise for objective RGC assessment. AI can be leveraged to analyze large datasets from OCT, OCTA, and electrophysiological tests, potentially identifying subtle patterns of RGC damage that are imperceptible to the human eye. AI could also assist in automating image segmentation, correcting artifacts, and providing more accurate and reproducible measurements. Furthermore, AI-driven predictive models could help stratify patient risk, forecast disease progression, and personalize treatment strategies based on individual RGC profiles.

Exploring Novel Neuroprotective and Regenerative Strategies. Objective RGC assessment methods are critical endpoints for evaluating emerging neuroprotective and regenerative therapies. Future research should continue to explore novel approaches such as gene therapy, stem cell transplantation, and neurotrophic factor delivery aimed at increasing RGC survival, promoting axon regeneration, and

restoring visual function. Objective functional and structural measures will be indispensable for assessing the efficacy of these interventions in preclinical models and clinical trials.

VII. Conclusions

The objective evaluation of retinal ganglion cell function is a cornerstone of modern ophthalmology and neuro-ophthalmology, driven by the inherent limitations of subjective visual field testing in detecting early RGC damage. RGCs, as the sole output neurons of the retina, are critical for vision, and their dysfunction or loss is central to numerous debilitating conditions, most notably glaucoma. The field has witnessed a continuous "resolution revolution", progressing from broad electrophysiological assessments to highly specific structural and microvascular imaging, and now to cellular-level visualization.

Pattern Electroretinogram (PERG), Visual Evoked Potentials (VEPs), and Photopic Negative Response (PhNR) provide objective functional insights into RGC activity, with PERG and PhNR demonstrating particular sensitivity to RGC dysfunction, often preceding detectable structural loss. Optical Coherence Tomography (OCT) and its advanced variant, OCT Angiography (OCTA), offer precise structural and microvascular quantification of RGC layers and their blood supply, proving invaluable for early diagnosis and monitoring.

Despite these advancements, significant challenges persist. The heterogeneity of RGC subtypes complicates comprehensive assessment, and the precise relationship between RGC dysfunction and irreversible cell death remains an area requiring further elucidation. Current methods face limitations related to technical artifacts, reproducibility, and the "floor effect" in advanced disease. Furthermore, the translation of cutting-edge technologies into routine clinical practice is hindered by high costs, technical complexity, and a lack of standardized normative databases. The ongoing debate regarding the "experimental" status of some promising electrophysiological tests highlights a critical translational gap that requires robust, large-scale validation studies.

Future research must focus on developing integrated multimodal assessment platforms, enhancing the clinical utility and accessibility of advanced imaging, investigating RGC subtype-specific biomarkers, conducting extensive longitudinal studies, and leveraging artificial intelligence for improved data analysis and clinical decision-making. These efforts, coupled with continued exploration of novel neuroprotective and regenerative therapies, will be crucial for advancing the early diagnosis, precise monitoring, and ultimately, the preservation of vision in patients affected by RGC pathologies.

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Posterior eye segment's fluid dysregulation in mechanism of optic nerve damage development (literature review)

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Abstract

The review highlights the current state of knowledge regarding fluid circulation in the posterior segment of the eye and its potential role in optic nerve damage. Compared to the anterior segment, the mechanisms governing fluid dynamics in the posterior segment remain underexplored. Recent hypotheses suggest that the retina and optic nerve possess their own clearance system, operating either autonomously or in conjunction with the brain's lymphatic system. This system is thought to facilitate metabolic waste removal through intraocular, cranial, and interstitial fluid exchange. A better understanding of these processes may contribute to improved diagnostics and novel therapeutic approaches for optic neuropathies.

Aim: To analyze literature data on the impact of impaired fluid circulation in the posterior eye segment on optic nerve damage mechanisms.

Methods: A systematic literature review of 44 sources.

Key findings: The optic nerve allows for bidirectional fluid exchange between the eye and brain. Under normal conditions, perfusion is maintained by the lamina cribrosa, the distribution of subarachnoid spaces, and aquaporin-4 (AQP4) channels.

The role of the ocular lymphatic system in optic nerve function remains uncertain. It is hypothesized that it may interact with the brain's lymphatic system, influencing intraocular, interstitial, and cerebrospinal fluid dynamics.

Disruptions in these processes may contribute to conditions such as high myopia, optic disc drusen, inflammatory optic neuropathies, and neurodegenerative diseases.

The slowing of fluid transport may coincide with reduced axonal transport, leading to the progression from neuropathy to optic nerve atrophy.

Conclusions: Dysregulated fluid circulation in the posterior segment of the eye may play a role in optic nerve damage. Enhanced diagnostic techniques focusing on ocular hydrodynamics could provide valuable insights into disease mechanisms. Furthermore, interventions targeting fluid regulation may offer therapeutic potential for optic neuropathies.

Key words: optic nerve, ocular lymphatic system, translaminar gradient, high myopia, optic disc drusen, inflammatory optic neuropathy.

Introduction

Most scientific research is devoted to the functioning of the anterior (so-called convection) pathway: the trabecular meshwork, juxtacanalicular tissue and Schlemm's canal and collecting ducts, from where the fluid flows into the episcleral venous system [1, 2]. The unconventional pathway of fluid outflow is through the uveoscleral space [3].

The transport and exchange of fluids (blood, intraocular, intercellular fluids, metabolic products) in the posterior part of the eye have their own characteristics compared to the anterior part of the eye. The disorder can be considered in the hypotheses of the development of both acute and chronic diseases of the choroid, retina and optic nerve.

Regarding the optic nerve, the question arises about the regularity and interrelationship of fluid circulation, perfusion and reperfusion, as well as axonal transport in the anti- and retrograde directions. Also, the understanding that the slowdown of such processes lies at the basis of the transformation of neuropathy into optic nerve atrophy, and therefore the possibility of restoring structure and function.

That is why the study of the features of fluid transport and exchange in the back of the eye is important in the study of diseases of the optic nerve, and the correction of disorders of such circulation could be used for therapeutic purposes.

The transport and exchange of fluids in the posterior part of the eye is less well understood than in the anterior part. An interesting theory is the lymphatic system of the eye, which explains the exchange and clearance of metabolic products of the choroid and retina through a system of interactions between intraocular, intracranial and intercellular fluids.

The authors of this theory borrowed data on the circulation of cerebrospinal fluid in the brain [4] and suggest that the purification of the retina and optic nerve from metabolic products may occur according to similar laws [5, 6].

The term brain lymphatic system was first introduced in 2012 (Fig. 1) [4]. According to the authors' theory, an experiment in mice has shown that cerebrospinal fluid enters the brain along periarterial channels for exchange with extracellular fluid, and extracellular fluid is removed from the brain via perivenous pathways, from where it moves to the lymphatic vessels of the neck and, ultimately, to the systemic circulation [4]. It is suggested that the perivascular spaces of the retina may provide a similar function in the eye as in the brain [7].

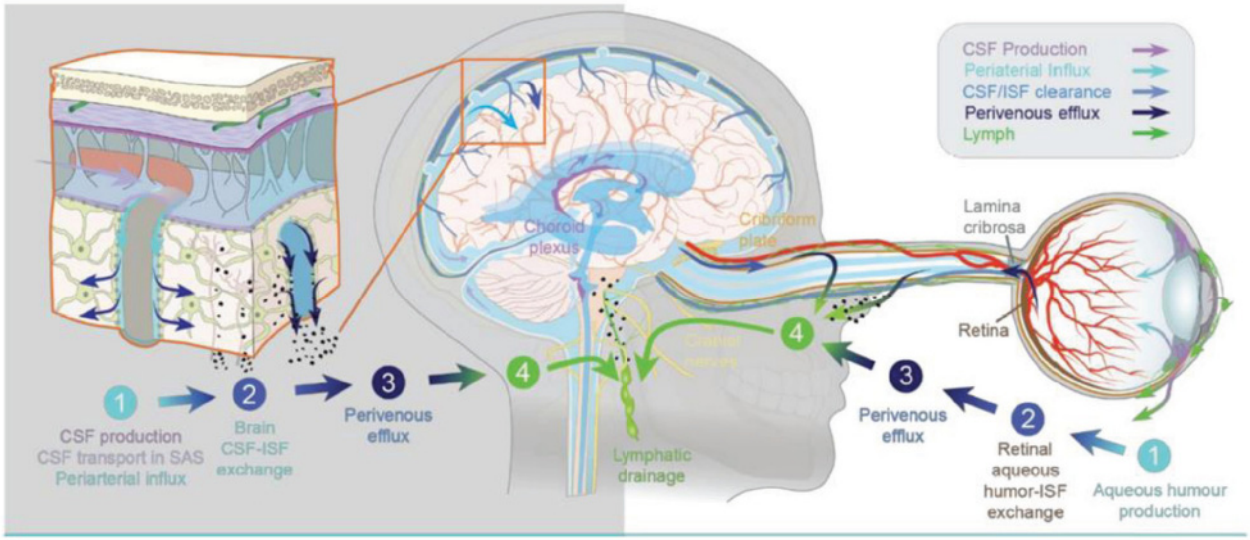

Fig. 1. The lymphatic system of the brain and eye. Legend: in the brain 1A cerebrospinal fluid (CSF) is produced and transported into the subarachnoid space, opens into the periarterial inlet; 2A in the brain there is an exchange of CSF and intercellular fluid (IMF); 3A perivenous outlet; in the eye 1 intraocular fluid is produced, 2 exchange of intraocular fluid with IMF in the retina; 3 perivenous outlet; 4A, 4 lymph nodes; 5 retina, 6 ethmoid plate, 7 lymphatic drainage, 8 cranial nerves, 9 choroid plexus [44].

Proponents, based on experimental studies, argue that the ocular glymphatic system in the posterior segment of the eye operates through four functional segments [8]. Aqueous humor is produced by the ciliary body (first segment) and enters the retina after passing through the vitreous humor (second segment).

The third segment - aqueous humor mixes with the interstitial fluid of the retina, and excess fluid is transported along the axons of the ganglion cells through the reticular lamina, from where the fluid spreads into the perivenous spaces and through the supporting aquaporins - 4-channels (AQP4).

Intraocular and intracranial pressures (translaminar gradient) are important in ensuring the transport of fluid through the reticular lamina. Light-induced pupil constriction accelerates the movement of intraocular indicators into the optic nerve, which is supported by smooth muscle pressure contractions, and also promotes fluid migration into the posterior compartment.

Fourth segment: Intraocular excretion markers (e.g., amyloid-ß) exit the eye along retinal ganglion cell axons and then enter the perivenous spaces with subsequent lymphatic drainage to the cervical lymph nodes.

The optic nerve also has a system that circulates cerebrospinal fluid in its various parts along the central retinal artery [9], and therefore, presumably, this is where the lymphatic system of the eye (the third and fourth components) and the brain mix or interact. In particular, it is known that intraocular fluid, intercellular fluid of the retina and brain, and cerebrospinal fluid circulate in the optic nerve, and therefore it is important to understand the mechanisms that provide a balance between them to ensure the functioning of the nerve.

The question arises whether the optic nerve has its own separate glymphatic system, or whether it interacts with the lymphatic system of the brain [8].

It is known that the fluid in the optic nerve spreads due to the peculiarities of the structure of the nerve itself and the position of the subarachnoid space, which in the bulbar segment consists of trabeculae (similar to the trabeculae in the anterior segment of the eye), in the middle orbital segment - of septa and pillars, and in the tubular part contains both trabeculae and pillars (Fig. 2) [11].

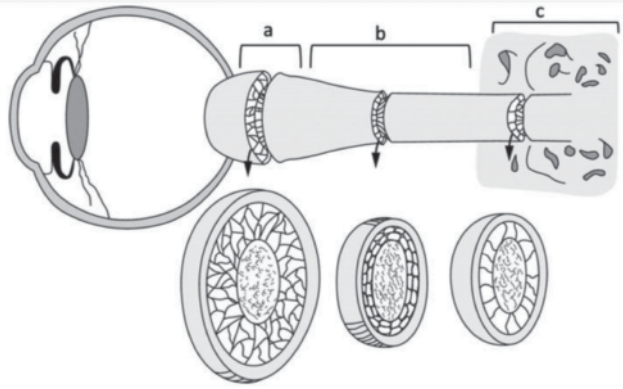

Fig. 2. Distribution of subarachnoid spaces in the intraocular (a), intraorbital (b) part and in the optic nerve canal (c).

It also remains unclear how the circulation of intraocular fluid, intercellular fluid of the retina and brain, and cerebrospinal fluid in the optic nerve coordinate with blood, and also change under conditions of atmospheric pressure fluctuations.

The expression of aquaporin-4, which belongs to the third segment of the glymphatic system of the eye, has been established in the retina and optic nerve [12], and is also interesting in the context of studying the possibility of developing optic nerve damage.

Thus, it can be assumed that disturbances in the circulation of fluids in the posterior segment of the eye may be among the hypotheses regarding optic nerve damage. Similar processes are studied in the pathogenesis of Alzheimer's disease, glaucoma [13] and age-related maculopathy [14].

We propose to consider the possibility of a similar mechanism in the development of acute optic neuropathies, which will subsequently make it possible to correct them.

The goal is to identify disorders of fluid circulation in the back of the eye in the mechanisms of optic nerve damage development, according to the literature.

Methods

Methods - literature search of 44 sources.

Results

Possible hypotheses regarding factors that lead to impaired circulation of fluids in the back of the eye. Translaminar circulation.

1) Deformation of the ethmoid bone, when it loses its ability to provide a balance between intraocular and intracerebral pressures [15].

The ability to tolerate pressure differences depends on many factors, such as the elasticity, stiffness, and geometry (thickness, shape, or curvature) of the lamina propria and connective tissue around the optic disc, which is determined by genetic predisposition, race, or age [16].

Eyes with a stiffer lamina may be more resistant to deformation. Eyes with a thinner lamina are more sensitive to deformation. Regardless of the sensitivity to deformation, a thinner lamina also contributes to increased translaminar pressure as a result of a reduced difference between the intraocular and retrolaminar spaces, which may limit both antegrade and retrograde axoplasmic transport [17].

2) High-grade myopia, when the eyeball is enlarged, leads to deformation and densification of the reticular lamina. It has been hypothesized that the complications of myopia may be due, to some extent, to inflammation. The authors suggest that multiple autoimmune foci of damage occur between the choroid layers [18].

In high-grade myopia, according to the author, the likelihood of multiple transient white spots syndrome and acute idiopathic blind spot enlargement syndrome increases. This is explained by the blockage of the exchange between intraocular and interstitial fluids and impaired cleansing of the posterior segment of the eye.

Multiple transient white spot syndrome which is of autoimmune origin, is characterized by unilateral yellowish-white foci on the fundus, slight swelling of the optic disc, decreased visual acuity, and visual field defects [19].

Idiopathic blind spot syndrome is characterized by normal visual acuity, fundus, and pupillary response. It causes scotomas in the projection of the optic disc. Electrical retinography in such cases reveals a decrease in the activity of the peripapillary retina. A similar phenomenon is also explained by the occurrence of inflammation and possible occlusion of the choroid capillaries around the optic disc, which presumably leads to impaired transport and fluid exchange in the posterior segment of the eye caused by secondary ischemia of the outer retina [20].

Under adverse conditions, when ischemia becomes more pronounced, compensatory non-dilation of the inner retinal vessels and vascular neoplasms are provoked [21, 22].

In severe cases, acute myopic optic neuropathy occurs [23]. In this case, in an enlarged eyeball with a dense sclera, the pressure of the episcleral veins (through which intraocular fluid flows) increases and the optic nerve is damaged [24].

Mechanical optic neuropathy results from critical atmospheric pressure fluctuations associated with air travel or deep diving in the presence of a deformed reticular formation. Symptoms are attributed to gravitational forces or acceleration-deceleration forces during aircraft landing [25]. Such forces can cause mechanical stretching of the already deformed and elongated optic nerve and eyeball, which occurs in high-grade myopia. This results in a transient decrease in acuity associated with changes in aqueous humor outflow [26].

It is believed that rapid acceleration during aircraft landing can cause a critical increase in venous pressure. This will cause blood to pool in the lower extremities, leading to ischemia and hypoxia of the brain and eyes with temporary loss of central or peripheral vision and loss of consciousness [27].

It is believed that the reticular formation, which should balance intrathoracic, abdominal, and cranial hydrostatic pressures, is stretched and thinned due to myopic morphological changes, and therefore loses its ability to tolerate. Therefore, the pressure gradient exerted on the deformed optic nerve leads to even more significant damage after increases in intracranial pressure caused by free fall during airplane landing or deep diving [28].

In the process of myopia progression, there is an increase in the aperture of the scleral flanging foramen around the optic disc, but the size of the nerve itself does not change. Thus, the posterior surface of the peripheral part of the ethmoid plate is exposed. Its shock-absorbing properties are lost in relation to the optic nerve head, which is exposed to the influence of orbital cerebrospinal fluid, which leads to acute optic neuropathy under conditions of critical fluctuations in hydrostatic pressure [29].

Optic nerve head drusen are often an incidental finding during fundus examination. They can be located superficially or in deep structures, even between the cells of the reticular lamina, limiting its shock-absorbing properties and hindering the circulation of fluids in the optic nerve.

In rare cases, drusen can combine and thereby worsen the situation in anterior ischemic neuropathy [30]. In this case, the tortuosity of the disc venules and capillary hemorrhages associated with stasis will contribute to the diagnosis of optic nerve edema. It is this edema of nerve fibers that serves as an additional factor in limiting fluid circulation in the posterior segment of the optic nerve. The exchange of intraocular and intercellular fluid is disrupted, as well as their transport into the venous collectors of the brain [31, 32]. The fibers are compressed, and axial transport in both the anti- and retrograde directions is impaired [33].

It is also believed that drusen may be a factor in the development of ischemic ocular lesions, such as central venous occlusion and neovascularization, which also occur under the influence of impaired fluid perfusion and the posterior segment clearance system of the eye [34].

It is noted that ischemic optic neuropathy, caused by optic nerve head drusen, occurs in younger patients and has a less favorable course [36].

Orbitopathy

Inflammation of the orbit, which includes both idiopathic diseases and the consequences of systemic or local inflammatory conditions. Often a consequence of neoplasms, infectious lesions, congenital malformations or trauma. Often combined with systemic inflammation of the thyroid gland, sarcoidosis, granulomatosis Wegener's, Crohn's disease, systemic lupus erythematosus, Churg-Strauss syndrome, Erdheim-Chester syndrome, histiocytosis X, and giant cell arteritis [37].

Paranasal sinuses

A. Perinasal sinus disease can cause conditions that mimic demyelinating optic neuritis, with acute optic neuropathy and pain on eye movement, or can cause progressive optic neuropathy due to compression [38].

B. Compressive optic neuropathy may be caused by mucoceles or mucopioceles of the ethmoid and/or sphenoid sinuses and/or associated swelling and thickening of the sinus walls. Polyps involving the mucosa of the sphenoid sinus also cause compression of the nerve. By causing swelling of the optic nerve, the paranasal sinuses [39] may also cause impaired fluid circulation in the posterior segment of the eye.

C. The local anatomy of the venous circulation in the orbital -apical region may also play a role in the pathogenesis of optic neuropathy associated with sinus disease. Optic neuropathy may be associated with the spread of cytokines and/or immune mediators from the sinuses to the orbital-apical part of the optic nerve via the local venous circulation with local vasomotor changes. Secondary inflammatory occlusive vasculitis also causes optic neuritis [40].

AQP4 plays a role in the circulation of the posterior segment of the eye, as it facilitates the passage of fluid from nerve cells into the intercellular space, as well as into the intermembrane spaces (Fig. 3).

Neuromyelitis optica Devika is a type of autoimmune disease of the central nervous system that damages the optic nerve and spinal cord [41]. In this case, damage to astrocytes causes marked swelling of axons, which may be the cause of myelin loss [42].

The role of the lymphatic system of the brain or eye in the development of neuromyelitis optica is still unclear, but it is known that in this case the immune system produces antibodies specifically to AQP4 channels along with edema of the optic nerve, which suppresses the lymphatic system of the eyes and brain [43].

Discussion

The optic nerve allows for bidirectional fluid exchange between the eye and brain. Under normal conditions, perfusion is maintained by the lamina cribrosa, the distribution of subarachnoid spaces, and aquaporin-4 (AQP4) channels.

The role of the ocular glymphatic system in optic nerve function remains uncertain. It is hypothesized that it may interact with the brain's lymphatic system, influencing intraocular, interstitial, and cerebrospinal fluid dynamics.

Disruptions in these processes may contribute to conditions such as high myopia, optic disc drusen, inflammatory optic neuropathies, and neurodegenerative diseases.

The slowing of fluid transport may coincide with reduced axonal transport, leading to the progression from neuropathy to optic nerve atrophy.

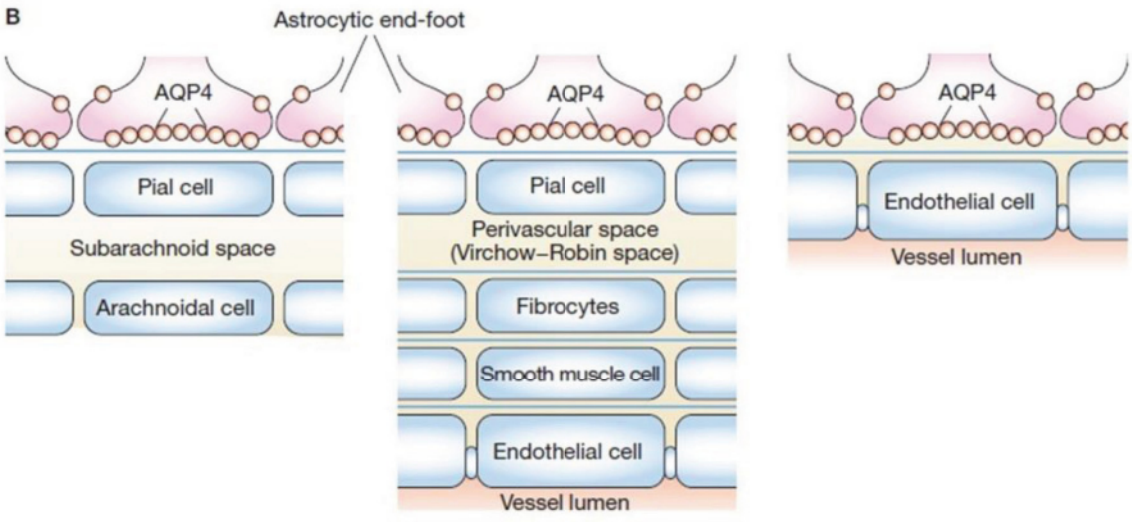

Fig. 3. The role of AQP4 in fluid circulation in the brain spaces.

Conclusions

Dysregulated fluid circulation in the posterior segment of the eye may play a role in optic nerve damage. Enhanced diagnostic techniques focusing on ocular hydrodynamics could provide valuable insights into disease mechanisms. Furthermore, interventions targeting fluid regulation may offer therapeutic potential for optic neuropathies.

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Conjunctival papilloma

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Abstract

An adult male presented with two distinct conjunctival papillomatous growths, one pedunculated and one sessile on his left lower lid. The patient was reassured that most of the time these masses turn out to be benign. He was recommended to wait and watch because frequently the growths regress spontaneously. Patient returned after about two years because both the tumorous papillomas had doubled their sizes were more angry looking. Patient was concerned about these being "cancerous". Surgical excisional biopsy was performed and the tumor bed had intra-operative cryotherapy. Histopathologically proven benign masses were caused by Human Papilloma Virus (HPV). A brief review of literature is attempted to highlight the fact that rarely such conjunctival papillomas may develop in adults as well, though more commonly seen in young children.

Key words: conjunctival neoplasia, conjunctival papilloma, viral papilloma, squamous papilloma, pedunculated, sessile, benign, recurrence, surgical removal, seeding of lesions, cryotherapy, interferon, mitomycin-C.

Introduction

Conjunctival growths are bothersome to both patient and the physician. Some growths such as Pinguecula and Pterygium [1 - 2] are quite common and very slow growing. Often, patients are not much concerned about these initially disfiguring growths. On the other hand, some growths such as papillomas, follicular concretions, chalazion granulomas etc. become worrisome to the patients because of their rapid growth and the concern of these being cancerous. Most of these conjunctival growths are usually benign but some turn out to be malignant. Either because of pain and redness associated with such growths or their rapid progression compels patients to seek medical help. Conjunctival papillomas [3 - 8] belong to the latter group; these look awful and their rapid growth is taken by the patients as "cancerous". I encountered such a case which is worth sharing with brief review of literature.

Case Report

A 56 years Afro-American, otherwise healthy male, initially presented with "something growing inside the left eye". He first noticed redness and something growing inside the left lower lid over a year ago. He denied any recent trauma, pain, redness, discharge, systemic tumors diagnosis, or exposure to any new sexual partner. Ocular examination was within normal limits and without any significant ocular findings. Vision and intraocular pressure were within normal limits.

Left lower tarsal conjunctiva had two globular papillomatous growths, one in nasal inferior fornix and close to caruncle, the second growth on the tarsal conjunctiva close to lid margin. These measured about 1.5 x 0.5 cm and 1.0 x 1.0 cm respectively. Based on the initial clinical examination, patient was explained and reassured that the growths or masses seemed papillomas, most likely benign and of viral etiology. Most of these growths are known to undergo spontaneous regression. But, the patient had already experienced these growths were not regressing spontaneously, rather were gradually growing bigger. Based on his history of gradual progression of both the lesions he was advised surgical excisional biopsy before those grew larger or implanted seeds for more papillomatous growths. Patient wanted to think it over and discuss with the family before scheduling surgical procedure.

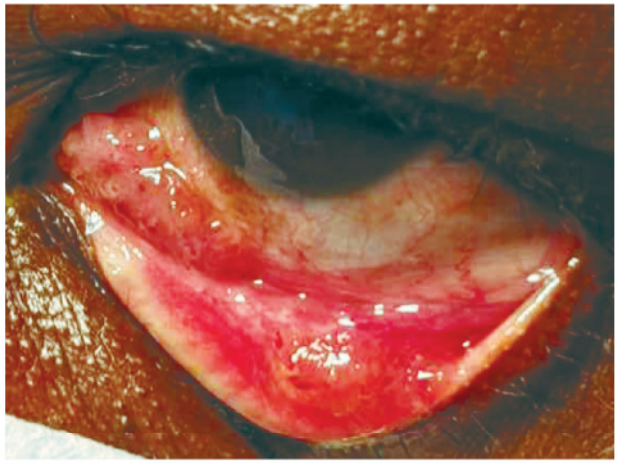

Fig. 1. Two distinct papillomatous neoplasia/ growths in left inferior fornix (within blue arrows) seen on initial encounter (June 2020).

It was almost two years later that the patient returned for reevaluation of the growths. The masses had grown significantly, exposed and extruding between the eyelids on lid closure all the time. Lately, he had been observing whitish discharge on the surface of the nasal growth. Cosmetically disfiguring mass with "infected appearing" discharge forced the patient to seek medical advice. On close questioning, patient revealed that he

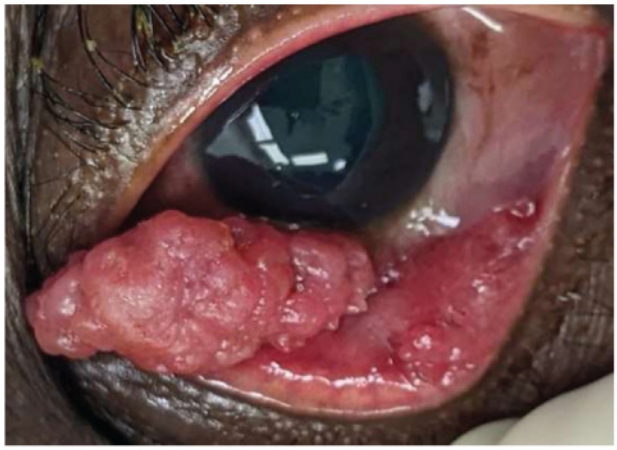

Fig. 2. Same two papillomatous neoplasia/ growths (within blue arrows) look confluent after about two years (April 2022).

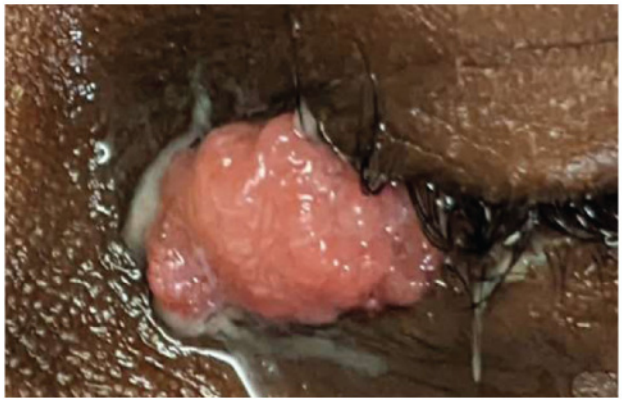

Fig. 3. Large papillomatous neoplasia (growth) with mucopurulent discharge extruding between the closed left eyelids forced the patient, after about two years, to seek medical help.

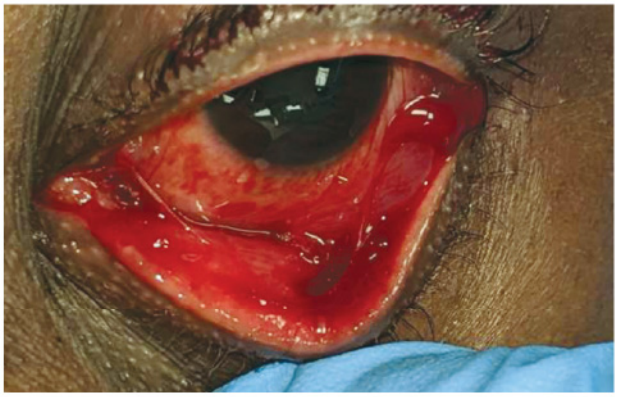

Fig. 4. Same left lower lid as seen immediately post-excisional biopsy of tumorous papillomas and local cryotherapy of the beds of both neoplasias.

did not have medical insurance or enough finances two years ago for the surgical procedure recommended. Also, patient took it less seriously when he was explained on initial visit that it appeared to be "benign growths". As he got medical insurance now and was getting concerned for it to be cancerous or infected with whitish discharge that he returned for proper management.

The clinical examination showed the nasal and fornix-based mass had grown to 2.5 cm x 1.25 cm pedunculated and the tarsal conjunctival mass had grown to 2.0 cm x 1.0 cm sessile tumors. There was no new papilloma on conjunctiva of either eye. Patient signed informed written consent for "excisional biopsy" of both the conjunctival papillomas while understanding the risks of recurrence and/or new mass or masses. Under local infiltration anesthesia, both masses were excised in one-piece each. Nasal pedunculated tumorous growth was excised without much dissection but the tarsal conjunctival growth required large sharp dissection to excise the entire mass. Hemostasis was achieved with thermal cautery without complications. Both tumor bases were treated with cryotherapy to prevent recurrences and to destroy any seedlings dropping from the primary tumors. The eye was treated with combination of antibiotics steroid ointment (neo-poly-dex ointment) three times a day for two weeks and then twice a day for another week. Histopathologic examination confirmed the growths to be of viral etiology and benign in nature. A month later, patient healed well and without any signs of tumor recurrence or new masses.

Comments

Conjunctival papillomatous neoplasia are more commonly seen in very young children [3 - 8]. Most of the time the culprit virus gets implanted onto conjunctiva of the newborn during its passage through the infected maternal birth canal [9]. This could lead to uniocular or binocular conjunctival neoplasia as solitary or multifocal masses. The virus is transmitted by direct contact as happens during parturition [3 - 9]. But, our patient is middle aged male adult. It suggests that it might have happened by contaminated hands or fingers during sexual contact. Though rare still papillomatous neoplasia of conjunctiva can be encountered in adults [3 - 8], as seen in our patient.

Human Papillomavirus (HPV) is one of the members of Papovavirus family of viruses [3 - 8, 10 - 15]. Conjunctival papillomas are most commonly caused by HPV 11 but HPV 6, 6a and 45 have also been associated with this neoplasia [3 - 8, 10 - 15]. HPV is tumorigenic and leads to benign cauliflower shaped or multipronged finger like angry looking growth; rarely is may change to be malignant. Most of the lesions are seen involving the caruncle or in its close proximity. The variant seen more commonly in adults could be sessile, not pedunculated, and mostly as a limbal mass [3 - 8]. The case in discussion had one pedunculated cauliflower shaped mass close to caruncle but growing from the inferior conjunctival fornix. The second lesion was sessile and spreading on the tarsal conjunctiva almost adjacent to the lid margin. Most of the times, the tumorous mass is a very slow growing mass. Usually, it is more disfiguring when it protrudes between the lids than its being malignant.

Our patient is a typical example of its slow growing nature. On his initial visit, patient had a significantly large sized mass that brought him to seek medical help. He was aware of only this nasal cauliflower shaped mass that was getting to be more and more disfiguring than causing any other symptoms. It had

been growing for at least over a year as patient could recall. He was even unaware of the small lesion on the tarsal conjunctiva almost in the middle of lower lid. During his second visit both the tumor masses had grown to be almost twice their size in about two years. These slow growing papillomatous masses, often being asymptomatic, are frequently ignored by the patients till they become large and disfiguring. Our patient had a similar history and was getting concerned when he started to have a whitish gray discharge in the nasal canthal area and on the growth in the affected eye.

The patients are initially reassured and recommended to wait and watch because most of the times these are "benign neoplasias". Also, it is known that frequently the lesions regress spontaneously over time [3 - 8, 16]. Surgery is postponed because of an associated potential risk of recurrences [3 - 8, 17 - 18], along with seeding and more lesions developing while excising the papilloma [3 - 8, 17 - 18]. This patient was accordingly reassured and recommended to watch the natural course of the initial lesions. As we saw, over next almost two years both the lesions did not regress, rather grew to double the size and became disfiguring. At that stage surgical excision and histopathology were indicated. Excisional biopsy was performed under local infiltrative anesthesia. The masses were excised in one piece each with due care not to leave behind the edges of the masses. Pre-operatively, the patient was made aware of the fact that despite the best efforts and clean dissection there were potential risks of recurrence and seeding with multiple secondary papillomas. After achieving hemostasis with thermal cautery the tumor bed was treated with cryotherapy to prevent recurrence or seeding problem. One month post-operatively there were no signs of recurrence or secondary papillomas from seeding.

Numerous modalities have been used as adjunct therapies to surgical excision of conjunctival papillomas, but mostly to treat recurrences or recalcitrant squamous papillomas [19 - 20]. These include dinitrochlorobenzene immunotherapy [19], intra-muscular Interferon injections [20 - 23], topical adjunct application of mitomycin-C after excision [24], oral Tagamet (Cimetidine) [25 - 26], Carbon-dioxide (CO_2) laser [27 - 28], cryotherapy [29], thermal and electrodessication and intralesional bleomycin [4] etc.

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Синдромни глаукоми в детска възраст

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Syndromic glaucoma in childhood

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Резюме

Глаукомата в детска възраст продължава да е сериозно и значимо очно заболяване от гледна точка на причините за слепота и ранна инвалидност по зрение в световен мащаб.

В съвременен аспект терминът „Синдромна глаукома“ (СГ) обединява глаукомите, причина за възникването на които най-често са патологични мутации в доказани гени. В някои случаи СГ може да бъде диагностицирана при новороденото дете, но в болшинството от случаите се диагностицира в по-късна детска възраст, а в някои случаи и при възрастни индивиди.

След 2000 година проучванията на корелациите фенотип-генотип и на корелациите генотип-фенотип на вродено детерминираните глаукоми са обект на широки проучвания и дискусии в световен мащаб.

В статията се представят съвременните клинико-генетични аспекти на някои от вродено-детерминираните очни и системни заболявания, асоциирани с глаукома в детска възраст. Споделен е 39-годишен личен опит.

Ключови думи: детска глаукома, синдромна глаукома, предносегментни дисгенезии, клинико-генетични проучвания.

Abstract

Childhood glaucoma continues to be a serious and significant eye disease in terms of causes of blindness and early visual disability world wide.

In a modern aspect the term „Syndromic Glaucoma“ (SG) encompasses glaucomas that are most often caused by pathological mutations in proven genes. In some cases, SG can be diagnosed in newborns, but in most cases it is diagnosed in later childhood, and in some cases in adults.

After 2000, studies of phenotype-genotype correlations and genotype-phenotype correlations of congenitally determined glaucomas have been the subject of extensive research and discussion world wide.

The article presents the contemporary clinical and genetic aspects of some of the congenitally determined ocular and systemic diseases associated with childhood glaucoma. 39 years of personal experience shared.

Key words: childhood glaucoma, syndromic glaucoma, anterior segmental dysgenesis, clinical-genetic studies.

Въведение

Детската глаукома има своите клинични и етиологични особености, които я отличават от глаукомата при възрастните - рядка очна патология, по-често е вродена, в някои от случаите може да има видима и без специална оптика патологична дисморфична очна симптоматика от предния очен сегмент (ПОС), глаукомната патология и синдромните изяви трябва да се търсят насочено, причините за възникването ѝ са най-често генетични [12, 13, 20, 21, 24, 29, 31, 32]. Детската глаукома (ДГ) съставлява общо 7% от слепотата при деца в световен мащаб [14, 34].

Информацията за глаукомата във всеки един от аспектите ѝ - клиничен, етиологичен, клинико-генетичен, социален, бе за пореден път осъвременена и надградена след 2000 година, включително у нас. Отдавна е известно, че глаукомна патология без оценка на вътреочното налягане (ВОН) и на състоянието на всички очни структури от ПОС и задния очен сегмент (ЗОС) не винаги е възможна и не е достатъчна за доказване на конкретната ѝ клинична форма, особено в детска възраст [12, 29, 31, 35]. Осъвременяването на класификациите за глаукома с международно приложение, широкото въвеждане и прилагането на нови, по-висок клас апарати и дигитални методи за диагностика на глаукомата (ОСТ, компютърна периметрия, пахиметрия, безконтактна тонометрия и др.) допринесоха за ранната ѝ диагноза, обяснението на патологичните глаукомни процеси, прецизираното лечение.

Клинико-генетичните аспекти на вродената глаукома (ВГ) са отдавна обект на проучвания, дискусии, представяне на научни форуми, надграждане, включително у нас [1 - 6, 11, 13, 16, 17, 19 - 23, 25, 28, 32]. След приключването на Геномните проекти за генно картиране на човешкия геном (2000; 2003) се откри нова ера - постгеномна ера за клинико-генетичното изучаване на причините за наследствените заболявания при човека, респективно за наследствените заболявания на зрителната система [2, 4].

Редица молекулярно-генетични проучвания доказаха, че хетерогенността и хетероалелността са причина за широк клинико-генетичен полиморфизъм (КГП) при някои форми на ВГ. Съвременните мултидисциплинарни проучвания на корелациите фенотип-генотип и на корелациите генотип-фенотип на вродено детерминираните глаукоми са обект на споделяния и дискусии в световен мащаб [3, 4, 6, 25].

Цел

Да се проведе съвременен преглед на синдромните форми на глаукома в детска възраст.

Материал и методи

Проведен е литературен обзор на достъпната литература по проблема „Синдромна глаукома". Представени са литературни данни за деца с доказана синдромна глаукома. Споделен е 39 години личен опит.

Кратък исторически преглед на термина Синдромна глаукома

Терминологията, свързана с глаукомата в детска възраст е разнообразна, започва от антично време с първото описание на двустранно сляпо дете с „големи побелели очи". Това описание се запазва до 70-те години на XIX-ти век, когато A. Pare (1866 г.) въвежда описателния термин „Буфталм" (очни ябълки с абнормна големина), за да се отдиференцира глаукомата от рождение, от описваната при възрастни глаукома. В началото на XX-ти век е въведен терминът „Вродена глаукома" (ВГ), а буфталмът се отбелязва като нейна основна и първа клинична находка [2, 15, 24, 32]. К. Пашев е първият офталмолог у нас (а и за страните в Европа), който отбелязва, че ВГ е причина за двуочна слепота сред проучените слепи деца у нас (1909 г.). Прилагайки пръв генеалогичния метод същият автор констатира, че ВГ се наследява по автозомно-рецесивен начин (АР), а при някои деца е съпроводена с други очни промени [1]. В достъпната чуждестранна литература до 40-те години на XX-ти век различни автори използват термините „Буфталм" или ВГ, и/или „Хидрофталм" (J. Anderson, 1939).

Терминът „Синдромна глаукома" е въведен през 40-те години на XX-ти век, за да се уточни, че ВГ, освен с буфталм, е съпътствана и с други очни увреждания и се проявява фамилно, което я отличава от глаукомата при възрастни индивиди, а начина на наследяването остава да е АР. През 1962 г. детските глаукоми се разглеждат като вродени и придобити (след травми, тумори, възпалителни заболявания и др.) и в Международната Класификация на причините за слепота официално влиза терминът „Буфталм" (синоним за ВГ). През 70-те години на XX-ти век следва въвеждането на нови термини и информация за глаукомата в детска възраст - „Глаукома на новороденото" (1967 г. - F. Costenbader), „Ювенилна глаукома" (1970 г. - R. Shaffer), „Детска глаукома" (1973 г. - W. Leydecker). През 1982 г. Shields въвежда термините Първична откритоъгълна глаукома (POAG) и Първична закритоъгълна глаукома (PACG), приети за международна употреба, а в последвалата нова класификация за глаукома ВГ се дефинира като Първична вродена глаукома, като е включена в групата на POAG. От 90-те години на XX-ти век до днес клинико-генетичните (КГ) форми на ВГ, като част от ДГ се обсъждат на ново ниво - в светлината на КГП, изучаван на органно, организмово и молекулярногенетично ниво, сведения за които има включително у нас [2 - 6, 9, 11, 16, 20, 25, 26, 32, 33]. В етиологията на детските очни аномалии и заболявания, включително на детската глаукома, се обсъждат екзогенни фактори (вродени инфекции - TORCH), унаследена мутация, генетична предиспозиция, спонтанни мутации, неуточнени случаи. Дискусиите за вродената очна патология (дисморфизъм), включително на ВГ, кореспондират с периодите на ембриогенезата, органогенезата и диференциацията на окото и организма, последователно във времето, на базата на анатомичната локализация на дефектите (конкретни заболявания и състояния) [2, 4, 24, 27].

В постгеномната ера терминът „Синдромна глаукома" в детска възраст обединява вродено детерминираните глаукоми, причина за възникването на които са патологични мутации в доказани гени на молекулярно ниво, с нови дигитални методи [9, 18]. В съвременните консенсусни клинични класификации на глаукомата терминологията, критериите за оценка на диагнозата, разделното класифициране на клиничните форми - за деца и за възрастни, насоките за приложение на глаукомата са унифицирани. В класификацията на ДГ вече съществува и терминът синдромна глаукома [12, 29, 35]. В 10-та и 11-та ревизия на Международната класификация на болестите при човека (МКБ-10; МКБ-11), която рутинно използваме в ежедневната си практика, ДГ е с общ код за всичките ѝ клинични форми. Липсва съвременна единна КГ класификация на ДГ. Насоченото проучване на корелациите фенотип-генотип и на корелациите генотип-фенотип на вродено детерминираните глаукоми в постгеномната ера са обект на изучаване с дигитални методи и споделяния с дискусии в световен мащаб [2, 3, 6, 11, 16, 22, 25, 30, 33]. Разностранна информация за глаукомата в детска възраст може да се намери в редица специализирани офталмологични, генетични и медицински списания, монографии, учебници, някои достъпни онлайн [1 - 26, 28 - 33, 35, 36].

Синдромни глаукоми

Клинико-генетичните форми на синдромните глаукоми с начало в детска възраст са две основни групи: I. Глаукоми при предносегментни дисгенези; II. Глаукоми при наследствени системни синдроми [12, 29].

I. Глаукома при предносегментни дисгенезии

Смутената морфогенеза е причина за абнормни промени в клетките на невралния гребен, имащи отношение към формирането на предната камера (ПК) и ПОС, а от там и причина за иридокорнеална симптоматика в постнаталния период, съпроводена с абнормно повишено ВОН.

Предносегментните дисгенезии, асоциирани с повишено ВОН или глаукома включват: Първична вродена глаукома, Предносегментни синдроми, Аниридия синдром.

Първична вродена глаукома

МКБ, 10: Q 15.0; H 40-42; МКБ-11: 9C6140; OMIM: 231300, 600975; 613085; 617272; ORPHA: 98976; GARD: 2485.

Първичната вродена глаукома (ПВГ), [Primary congenital glaucoma (trabeculodysgenesis)], е рядко очно заболяване в световен мащаб, макар честотата му да показва географски различия от 1:2500, в средно източните страни; 1:10 000 - 1:12 000 в западните страни; 1/18000 - 1/30000 в Европа. При кръвно родство на родителите честотата е от 5 до 10 пъти е по-висока [7, 8, 10, 12, 17, 20]. ПВГ е най-честата клинична форма на ДГ [3, 7, 8, 20, 21]. В периода на новороденото (0 - 1 месец) е рядко описвана, най-често се среща при деца до 3-годишна възраст, но в някои случаи е описвана и след 3 - 5 годишни деца, с видима изява на буфталм, сълзене, блефароспазъм. По-често се среща при момчетата (65%), в 70% е с двустранна изява. Суспектните за глаукома промени от ПОС са много и различни по данни на различните автори [3, 8, 17, 24, 32]. Очните промени в роговицата (оток) и в зрителния нерв (оток) след своевременно проведеното лечение и нормализиране на ВОН имат реверзибилен характер. Затова ранната клинична диагноза и своевременното оперативно лечение имат съществено значение за предотвратяване увреждането на невроганглийните клетки в ретината и зрителния нерв. Има описани случаи на деца с ПВГ и със спонтанна реверзибилност на някои от промените дори без оперативно лечение. Болшинството от случаите на деца с ПВГ са спорадични, от фамилните 10 - 40% са при кръвно-родствени бракове. Фамилните са с АР начин на наследяване и вариабилна експресивност от 40 до 100% от случаите [10, 25]. При ПВГ съществува впечатляваща хетерогенност. Различни смущения в генетичната регулация на окулогенезата в резултат на мутации на гени в различни генни локуси са доказана причина за различните субтипове ПВГ от A - E (до 2025 г.): 1. GLC3A (CYP1B1 ген, 2p21 (1995); 2. GLC3B (CYP1B1 ген, 1p36-36.1 (1997); 3. GLC3C (CYP1B1 ген, 14q24.3 (2002); 4. GLC3D (LTBP2 ген, 14q24.3); 5. GLC3E (TEK ген, 9p21.2 (2016), [3, 6, 10, 11, 16, 17, 20 - 22, 25, 30]. Мутациите в CYP1B1 gene включват 87% от фамилните случаи и 27% от спорадичните. По последни данни в гена CYP1B1 са констатирани 147 мутации, които включват missense, nonsense, frameshift, терминаторни мутации, делеция и вмъкване със значителна хетерогенност [10]. Тези мутации са причина за различни по степен дефекти в развитието на трабекуларната мрежа и създават условие за повишаване на ВОН и ПВГ. Молекулярно-генетично изследване при някои деца у нас с ПВГ доказва мутации в гена CYP1B1, а при деца от ромски произход са доказани мутации и в гена LTBP2 (Latent transforming growth factor beta binding protein), който принадлежи към групата на протеините на екстрацелуларния матрикс и е хомолог на фибрилина 1 гена [6, 25, 28]. В достъпната литература има публикации на деца с ПВГ и асоциация с други очни патологични находки или със системни заболявания и мутации в LTBP2 гена, което е основанието да се предполага, че се касае за ПВГ-синдром [22, 30].

Глаукома при предносегментни синдроми

МКБ-10: Q13.9.

Терминът Предносегментен синдром включва описаните вродени (дисморфични) очни находки в началото на XX-ти век от A. Peter (1906), след него от Axenfeld (1920), от Rieger (1930, 1935), които засягат структурите на ПОС и са причина

Табл. 1. Симптомокомплекс на Предносегментните дисгенетични синдроми (ПСДС).

ОЧЕН СИМПТОМОКОМПЛЕКС	ПСДС							
Тип	1	2	3	4	5	6	7	8
1. Широка и предно разположена линия на Швалбе (заден ембриотоксон)	+	+	+	+	+	+	+	+
2. Структурни промени в иридокорнеалния ъгъл	+	+	+	+	+	+	+	+
3. Повишено вътреочно налягане (37.0 - 70%)	+	+	-	+	+	+	+	+
4. Вродени промени в размерите на роговицата: микрокорнея (често) или буфталм (като усложнение)	+	+	-	+	+	+	+	+
5. Вродени роговични мътнини (макули, левкоми) с или без дефекти на десцеметовата мембрана	+	+	-	-	+	+	+	+
6. Хипоплазия на мезенхималния слой в ириса	+	+	-	+	+	+	+	+
7. Вродени предни синехии	+	+	-	+	+	+	+	+
8. Вродена коректопия	+	+	+	+	+	+	+	+
9. Вродена поликория	+	+	-	+	+	+	+	-
10. Вродени цепковидни зеници	+	+	-	+	+	-	-	+
11. Рефрактивни грешки:	+	+	-	+	+	-	-	-
а) хиперметропия (висока степен), с или без астигманизъм > 1.5 дсфе	±	±	±	±	±	±	±	±
б) миопия (от детска възраст), с или без астигматизъм > 1.5 дсфе	±	±	±	±	±	±	±	±

за повишено ВОН. Във времето до днес информацията се допълва и разширява, а в чест на Peter, Axenfeld и Rieger синдромите носят имената им [11, 16, 17, 20, 23, 24, 30, 32]. На Табл. 1 е представен съвременният симптомокомплекс, включващ основните дисморфични очни находки в ПОС при предносегментните дисгенезни синдроми (ПСДС), които затрудняват дренажния отток на ВОТ.

Всяка една от посочените в Табл. 1 очни стигми може да е едностранно или двустранно изявена, като при двустранното наличие може да съществува една и съща или различна степен на клинична изява, различни съчетания на две или повече очни находки при един болен, различна динамика на изявите във времето. Всичко това е повод да се предполага съществуването на общ патофизиогенетичен механизъм, свързан с развитието на иридокорнеалния ъгъл. Съчетанието на очните промени и асоциацията им с общи или системни заболявания е обект на насочени проучвания за доказването дали първопричината е само генетична или влияние оказват епигенетични, смесени и/или други екзогенни фактори [2, 11, 18, 20, 23, 32]. Терминът Предносегментна дисгенеза (ПСД) [Anterior segment dysgenesis (ASGD)] в чисто клиничен аспект включва всички вродени очни аномалии в предния очен сегмент. Касае се за рядка очна патология. ПСД като цяло крият 50% риск за развитие на глаукома [23]. Клиничното многообразие, спорадичния характер в болшинството от случаите, широката диференциална диагноза, както и малката възраст на болшинството от изследваните деца и необходимостта от изследването им под обща анестезия и невъзможността за прилагане на дигиталните офталмологични методи за диагностика на глаукомата в невербална възраст са основна причина за затруднения в ранната диагноза. Терминът синдроми при ПСД или ПСДС в клинико-генетичен аспект обединява всички описани (до сега) очни синдроми, при които се отчита затруднение в дренажния отток на ВОТ и глаукома (синдром на Peter, синдром на Axenfeld, синдром на Rieger, синдром на Axenfeld-Rieger, допълнени от други автори), причина за възникването на които са доказани мутации в конкретни гени. ПСДС включват хетерогенна група от осем клинико-генетични варианти, с препокриваща се клинична изява, представени на Табл. 2, които включват описаните в Табл. 1 очни прояви в различни комбинации, но в етиологичен план се различават. Последни проучвания на пациенти с ПСДС доказват наличие на мутации в нови гени: гена Collagen 4A1 (COL4A1) и гена Beta-1.3-glucosyltransferase (B3GALTL), които кодират колагеновата верига, отговорна за образуването на базалните мембрани [20, 23].

Използването на нови технологии, като секвениране/сравнение на целия геном геномна хибридизация, има вероятност да разшири спектъра на мутации в известни гени и да подпомогне идентифицирането на нови причиняващи гени, както и модификатори, обясняващи фенотипа променливост на състоянията на ПСД.

Аниридия синдром

Терминът Аниридия синдром е съвременен и включва случаите на Вродена изолирана аниридия и Вродена аниридия, свързана със системни увреждания или Аниридия плюс синдром. Аниридия плюс синдром е разгледана в раздел II на тази статия.

Табл. 2. Клинико-генетична класификация на Предносегментните дисморфични синдроми (ПСДС) [OMIM, Cheong et al., 2016].

Предносегментни дисморфични синдроми (ПСДС) - тип	OMIM	Ген/Хромозомна НУ*		
		Координация	Локализация	
ПСДС - тип 1	07250	PITX3 (602669)	10 (10q24.32)	АД
ПСДС - тип 2	610256	FOXE3 (601094)	1p33	АР
ПСДС - тип 3	601631	FOXC1 (601090)	6 (6p25.3)	АД
ПСДС - тип 4	137600	PITX2 (601542)	4 (4q25)	АД
ПСДС - тип 5	604229	PAX6 (607108)	11 (11p13)	АД
ПСДС - тип 6	617315	CYP1B1 (601771)	2p22.2	АР
ПСДС - тип 7	269400	PXDN 605158	2p25.3	АР
ПСДС - тип 8	617319	CPAMD8 (608841)	19 (19p13.11)	АР

* НУ - начин на унаследяване: АД - автозомно-доминантно; АР - автозомно-рецесивно.

Вродена изолирана аниридия

МКБ-10: Q13.1; МКБ-11: LA11.3; OMIM: 106210; 617142; 617141; ORPHA: 250923; GARD: 5816.

Синоним на вродената изолирана аниридия (Aniridia congenital isolated)

Първо клинично описание на вродената тотална двустранна липса на ирис дава Barratta (1819), а у нас - К. Пашев (1943). Описани са единични случаи на едностранна изява.

Честота: 1 : 40.000 - 1 : 100.000, честотата на глаукома е 6% до 75%, като глаукомата до 13-годишна възраст е 26.5% и 75% при децата над 13-годишна възраст [20]. В причините за слепота у нас двустранната изолирана аниридия е 8.1% в УДНЗ (1984).

Допълнителни очни промени, съпътстващи аниридията са фотофобия, нистагъм, микрофталм, микрокорнея, роговични мътнини, роговична хипоестезия, страбизъм, централни точковидни катаракти, сублуксирани лещи, колобома на лещите, промени в папилата на зрителния нерв, повишено вътреочно налягане, рефрактивни промени самостоятелно или комбинирано проявени, от незначителни до силно проявени, миопия, хиперметропия, хипоплазия на макулите, ниско зрение [2, 20, 24, 32, 33]. Поради всичко това някои автори употребяват за вродената изолирана аниридия термина аниридия-синдром. В етиологичен план вродената аниридия включва 3 клинико-генетични варианти с припокриваща се клиника на изолираната аниридия, но с различна причина за възникване на патологията: I. Аниридия тип 1: Мутациите на PAX6 гена (11p13) в следните категории: 1. nonsense мутации (37%); 2. frameshift делеции или инсерции (23%); 3. сплайс мутации (11%); 4. missense мутации (18%); 5. anti-termination (run-on) мутации (4%); 6. in frame делеции или инсерции (7%); II. Аниридия тип 2: Мутации в PAX6 гена (11p13) и ELPA гена (11p13). III. Аниридия тип 3: Мутации в TRIM44 гена (11p13). Ние наблюдавахме дете, спорадичен случай, с вродена двустранна изолирана аниридия синдром, с доказване на мутация в гена VSH1 (Visual system homeobox1), неописвана в достъпната литература [2].

II. Глаукома при наследствени системни синдроми в детска възраст

Повишеното ВОН и глаукомата асоциирана с някои наследствени системни синдроми в детска възраст може да бъде един от първите клинични прояви в периода на новороденото, но най-често се констатират в хода на уточняването на синдрома или като последица от късната му диагностика. Представяме някои от описваните в достъпната литература наследствени синдроми асоциирани с глаукома в детска възраст: Аниридия плюс синдром (Синдром WAGR; Синдром WAGRO; Синдром на Gillespie); Синдром на Марфан, Синдром на Стърдж-Вебер, Неврофиброматоза синдром; Хомоцистинурия; Синдром на Льове; Синдром на Вайл-Марчезани; Синдром на широките палци [2, 9, 12, 16, 18 - 21, 23, 24, 30, 32, 33, 36].

Аниридия плюс синдром

Терминът Аниридия плюс синдром е съвременен и означава асоциация на вродената изолирана аниридия (аниридия синдром) със системни увреждания. Клиничният очен фенотип - аниридия синдром и глаукомно увреждане при всички описани аниридия плюс синдроми се припокрива, но причина за възникването им най-често е мутации в различни гени. По-често описваните от тях, макар и много редки заболявания, са синдромите WAGR, WAGRO и синдромът на Gillespie. В достъпната литература информация за асоциацията вродена аниридия с неврологична симптоматика включва над 20 описани спорадични случаи.

Синдром WAGR

МКБ-10: C64; МКБ-11: LD2A.Y; OMIM: 194072; 612469; GARD: 5528.

Синдром WAGR (Wilms tumor-aniridia-genital anomalies-retardation syndrome) представлява форма на спорадична вродена аниридия, характеризиращ се с делеция на късото рамо на хромозома 11 (11p13). И двамата родители имат нормални хромозоми. При децата със синдрома на WAGR съществува висок риск за развитие на тумор на Wilm's (билатерален тумор на бъбреците), генитални аномалии (крипторхизъм, аномалии на матката, гонадобластома, неразвити яйчници), както и умствена изостаналост (IQ < 74), най-често свързана с наличие на големи делеции и с честота 45 - 60% от боледуващите с аниридия.

Синдром WAGRO

OMIM: 612469.

Клиничният очен фенотип на синдром WAGRO (Wilms tumor-aniridia-genital anomalies-retardation obesitas syndrome) се припокрива с този на синдрома WAGR и включва вродена двустранна аниридия (аниридия синдром), към която по-късно (обикновено към 5-годишна възраст) се добавят туморът на Wilms (билатерален тумор на бъбреците), аномалии в генито-уретралната система, изоставане в психомоторното развитие и абнормно тегло (затлъстяване). Цитогенетичната локализация е върху късото рамо на хромозома 11 (11p13-p12), с геномна координация (GRCh38): 11:31 000 000 - 43 400 000. Етиологията е делеция в късото рамо на хромозома 11 (11p13-p12) в региона, който обхваща гените WT1 (607102), PAX6 (607108), и BDNF (113505).

Синдром на Gillespie

МКБ-10: G11.0; OMIM: 206700; GARD: 13.

Честотата на Gillespie синдром е <1/1 000 000. В литературата са описани около 30 случая. Клиничният очен фенотип на Gillespie синдром (GLSP) включва двустранна аниридия от рождение (аниридия синдром), към която по-късно се проявяват церебеларна атаксия и изоставане в психомоторното развитие. Описан е от Gillespi (1965). Кариотипът е нормален. Етиология е хетерозиготна мутация в гена ITPR1 (147265), картиран върху късото рамо на 3-та хромозома (3p26). Типът на унаследяване може да е АД или АР.

Синдром на Марфан

МКБ-10: Q87.4; OMIM: 154700; 610168; ORPHA: 558.

Синдромът на Марфан (Marfan's syndrome), описан от Williams (1876) и A. Marfan (1896), чието име до днес носи този синдром, е рядко системно заболяване на съединителната тъкан, с ниска честота (1: 3000 - 5000 души; 1-5:10 000). Диагностичните критерии са международно уточнени (1996 г.). В международен план са описани 1000 пациенти с този синдром. Причина за синдрома на Марфан са мутации в гена фибрилин (FBN1), картиран на 15 хромозома (15q21.1, 1991). В 15 - 30% от случаите се касае за нововъзникнали мутации, при фамилните случаи наследяването е АД. По литературни данни на различни автори очните промени са много, началото им е от 2-годишна възраст, а честотата им при отделните пациенти е различна (енофталм; анти-

монголоидни клепачни цепки; trabeculodysgenesis; плоска роговица; хипоплазия на ириса; хетерохромия; ранна катаракта; ектопия на лещата (54 - 80%); късогледство (53%); увеличена аксиална дължина на булба; отлепване на ретината; глаукома с ранно начало (най-често към 13-та година - 2% и вторични глаукомни усложнения към 30 годишна възраст). В наши проучвания на пациенти със синдрома на Марфан сред различни контингенти деца са били 6.5% деца (от 320 слепи деца с различни доказано наследствени заболявания, А. Попова 1984; 15 деца-пробанди, по данни на клиничен материал за 1984 - 2023, А. Попова [2]. Очната симптоматика е разнообразна, с различно начало на клинична изява, ход и тежест при отделните болни, което е причина за широк клиничен полиморфизъм. Това създава диференциалнодиагностични проблеми. По правило синдромът на Марфан е прогресираща патология.

Синдром на Стърдж-Вебер

МКБ-10: Q85.8; МКБ-11: LD23; OMIM: 185300; ORPHA: 3205; GARD: 7706.

Синдромът на Стърдж-Вебер [Sturge-Weber syndrome (SWS)] е описан за първи път от W. A. Sturge (1879) и F. P. Weber (1922 г.), чиито имена синдромът носи до днес, SWS представлява първична венозна дисплазия с липса на повърхностните дренажни вени в мозъчната кора, в периода 4 - 8 г.с. Честотата е различна (1 - 9/100 000 живородени). Заболяването най-често е спорадично, полът няма значение, липсва расова предилекция. Етиологията е мутации в гена GNAQ (Guanine nucleotide-binding proteins), хромозомна локализация 9q21.2. Типът на унаследяване на SWS е АД, с непълна пенетрантност и вариабилна експресивност. Липсват цитогенетични промени. Не са констатирани пренатални маркери. Съвременната класификация на SWS (Tortori-Donati et al. 2005) включва три типа: Тип I (класически), с кожни, лептоменингеални и очни промени (15 - 20% от пациентите, включват кожни ангиоми, известни като „nevus flammeus" или „port wine stain" от рождение; глаукома (30 - 90% от случаите, вторична от неоваскуларен тип), тип II, с кожни и очни промени (като при тип I) и тип III (фрустни форми), с лептоменингеални промени. Очната симптоматика при SWS е налице, когато присъства лицев хемангиом. Задължителни очни промени са хемангиом на клепачната кожа и глаукома, като последната може да се констатира на различен етап след раждане на боледуващия до 25-годишната му възраст. Описани са и други очни проблеми. При изследваните от нас 10 деца със SWS във времето всички притежаваха глаукома [2]. На Фиг. 1. е представен фрагмент от лицето на едно от изследваните деца (собствено наблюдение) със SWS, едностранен хемангиом, буфталм и глаукома, а на Фиг. 2 е представена част от засегнатата кожа и на едната ръка на същатото дете.

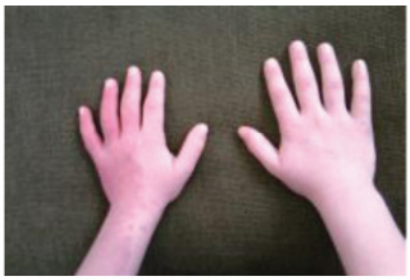
В диференциалнодиагностичен план, SWS е най-често срещаната факоматоза и единствената факоматоза, която не е асоциирана с вътречерепни неоплазми. От факоматозите фенотипно най-близък до SWS е Bonnet-Dechaume-Blanc syndrome (ретиноангиоматоза).

Неврофиброматоза синдром

МКБ-10: Q85.0; МКБ-11: L81; OMIM: 101000; 162200; 162210; 613675; ORPHA: 636; 637; GARD: 7866.

Неврофиброматоза синдром (Neurofibromatosis - NF), описана за първи път от Friedrich v. Recklinghausen (1833-1910) и до днес се употребява с названието Болест на Recklinghausen. NF е хетерогенна група моногенни редки заболявания (обща честота 1 - 5/10 000 новородени), при които се наблюдават неврофиброми с различна органна локализация, включително очна и пигментации по кожата тип „café au lait". Поставянето на диагнозата NF е въз основа на

Фиг. 1. Дете с едностранен лицев хемангиом, буфталм и глаукома (собствено наблюдение).



Фиг. 2. Кожен хемангиом на едната ръка при детето от Фиг. 1.

съвременни критерии, уточнени в Guidelines for the diagnosis and management of individuals with neurofibromatosis (2007). Описани са 6 КГ варианти на NF, най-честият от които е NF1. Начинът на унаследяване при всички КГ форми и варианти е АД. Очни прояви има описани при NF тип 1 и NF тип 2. NF тип1 се дължи на мутации в гена неврофибромин 1(NF1), картиран на 17-а хромозома (17q11.2), с над 300 мутации в него, като в около 50% от случаите мутациите са спонтанни (нововъзникнали мутации, АД). Очната симптоматика на NF тип 1, известна като периферна неврофиброматоза, включва фибромни промени по кожата на клепачите, най-често от рождение, в зрителния нерв (глиоми), в булба или орбитата, пигментирани фиброми - „петънца на Лиш" (описани от Karl Lisch 1973) по ирисите с честота 80 - 94%, които могат да са причина за глаукома в някои случаи, както и за промени в хориоидеята. NF тип 2 се дължи на мутации в ген, картиран в 22-ра хромозома (22q12), кодиращ протеина мерлин (merlin). Parry et al. (1994) предполагат, че NF тип 2 е хетерогенна патология. Очните промени при NF тип 2, известна като централна NF, се наблюдават извънредно рядко, липсват промени в ириса, но при възрастни пациенти са описани пресенилна задна субкапсуларна или нуклеарна катаракта и/или ретинални хамартоми (Pearson-Webb et al. 1986; Parry et al. 1994).

Синдром на Пиер Робин

МКБ-10: Q87.0; OMIM: 261800; ORPHA: 718.

Синдромът на Пиер Робин [Pierre's Robin Syndrome (PRS)] включва множествени вродени аномалии на лицевия череп, включително очни аномалии, обструкция на горните дихателни пътища, аномалия на небцето (cleft palate), гастроезофагеален рефлукс от рождение. Честотата е ниска, от 1:8500 до 1:14 000; 1 - 9/100 000. (Orphanet)]. Етиология включва мутации в ген с локализация 17q24.3-q25.1. Типът на наследяване е АР. Секвенирани са 4 кандидат-гени: SOX9, KCNJ2, KCNJ16 (605722), MAP2K6. Очните промени са разнообразни. За глаукома, отлепване на ретината, катаракта и миопия при синдрома на Пиер Робин съобщават B. Cosman и J. Keyser (1974). Диагнозата се основава на клиничните прояви, изявени след раждането и свързани главно с респираторните проблеми и гастроезофагеалния рефлукс. Синдромът на Пиер Робин се среща изолирано или като част от Stickler Syndrome, Velocardiofacial syndrome, Fetal Alcohol Syndrome, Treacher Collins Syndrome.

Хомоцистинурия

МКБ-10: E72.1; OMIM: 236200; ORPHA: 394.

Хомоцистинурията (Homocystinuria) е метаболитно наследствено рядко заболяване на аминокиселината метионин (при класическата форма), което се характеризира с повишена концентрация на хомоцистеин в кръвта и урината или дефицит на кофакторите (витамин B6, B12 и B9), поради липса или дефицит на ензимите, които нормално метаболизират хомоцистеина. Честотата за скринирани с биохимични тестове новородени за CBS (Cystathionine beta synthase) дефицит е 1 - 9:100 000 и 1:20 000. Над 92 различни патологични мутации в CBS гена са причина за два основни клинични фенотипа - пиридоксин отговорен и пиридоксин негативен. Генът CBS е картиран на 21-ра хромозома (21q22.3). Типът на наследяване е АР. Биохимичните промени включват увеличаване на хомоцистина и метионина. Към момента на раждането пациентите са фенотипно здрави, но при оставените без лечение се наблюдават различни патологични промени. Общата симптоматика се проявява в първата и втората декада от живота на боледуващото дете. Очната симптоматика включва: светли ириси, ектопия на лещата, която води до глаукома (до 85% при класическата форма) в различна възраст при някои пациенти, миопия от детска възраст, атрофия на зрителния нерв, отлепване на ретината. При нелекувани пациенти тази симптоматика е почеста. Диференциална диагноза на заболяването се прави с различни генетични и негенетични заболявания.

Синдром на Льове

МКБ-10: E72.0; МКБ-11: 5C60.0; OMIM: 309000; ORPHA: 534; GARD: 3295.

Синдромът на Льове (Lowe's syndrome) или Окуло-церебро-ренален синдром [Oculocerebrorenal syndrome (OCRL)], описан първоначално от Lowe, Terrey и MacLachan (1952), е рядко мултисистемно заболяване, което включва основно лицев дисморфизъм, първично увреждане на очите, на бъбреците (бъбречна тубулна дисфункция с хронична бъбречна недостатъчност) и централната нервна система (гърчове), забавяне в растежа, вследствие на ензимен дефект (phosphatidylinositol 4.5 - biphosphate 5-phosphatase дефицит). Честотата е ниска (1 - 9/1 000 000 и очаквана 1:100 000 до 1:500 000 новородени момчета [ОМИМ, ORPHA]. Етиология: Мутации в OCRL гена, картиран върху Х-хромозомата (Xq25-q26), наследяването е по Х-свързан рецесивен начин. Очните промени включват роговични мътнини, вродена двустранна катаракта, глаукома с или без буфталм, страбизъм, хиперметропия.

Синдром на Вайл-Марчезани

МКБ-10: Q87.0; OMIM: 277600 608328 614819; ORPHA: 3449.

Синдрома на Вайл-Марчезани (Microsherophakia, Weill-Marceshani syndrome - WMS, описван и като Spherophakia-brachymorphia syndrome, е рядко заболяване на съединителната тъкан, което се характеризира с нисък ръст, brachydactyly, скованост на ставите, аномалии на лещата. Честотата е ниска (1 - 9/100 000). Заболяването е хетерогенно, наследяването е предимно АР и рядко АД (Faivre et al. 2003), като не са констатирани значими фенотипни различия между пациентите с АР от тези с АД форма. Доказани са 3 КГ варианта на WMS. WMS 1 (АР) се дължи на хомозиготна или хетерозиготна мутация в ADAMTS10 гена, картиран на 19 хромозома (19p13.2). WMS 2 (АД форма) се дължи на мутация в FBN1gene, локализиран върху 15-а хромозома (15q21). WMS 3 (АР) се дължи на мутация в LTBP2 gene, локализиран върху 14-а хромозома (14q24). При т. нар. подобни на WMS пациенти са установени мутации в ADAMTS17 gene, локализиран също на 15-а хромозома (15q24). Въпреки генетичната хетерогенност при WMS съществува клинична хомогенност. Очната симптоматика, независимо от КГ форма включва микросферофакия, ектопия на лещата, промени в иридокорнейния ъгъл (45.2%), глаукома, дегенеративна високостепенна миопия, хетерохромия, катаракта. Усложненията на недиагностицираната и/или нелекувана своевременно ектопия на лещата водят до глаукома. Последиците са причина за тежки дефинитивни зрителни увреждания (до слепота).

Синдром на широките палци

МКБ-10: Q87.2; OMIM: 180849; 610543; 613684; ORPHA: 783.

Синдромът на широките палци (Broad thumbs-halluces syndrome), известен още като Rubinstein-Taybi syndrome е генетично мултисистемно заболяване, което се характеризира с лицев дисморфизъм, широки палци на ръцете и краката, нисък ръст, ниско тегло към момента на раждане. Честотата е ниска (1/125 000 - 300 000 раждания; 1 - 9/100 000 [по ORPHA]. Мутации в гена CREBBP са причина за заболяването. Генът е локализиран върху 16-а хромозома (16p13.3). Описани са 8 алелни варианта на този ген.

Очната симптоматика е разнообразна и включва птоза на клепачите, страбизъм, вродена глаукома, колобоми (на

ирис, хориоидея, ретина, зрителен нерв), рефрактивни грешки (високостепенна миопия), аномалии на слъзоотводните пътища, нистагъм, зенични аномалии, микрокорнея, микрофталм, роговични аномалии, атрофия на ириса, вродена катаракта, ектопия на лещата, микрофакия, хориоретинална атрофия, атрофия на зрителния нерв, аномалии на зрителния нерв. При отделните пациенти могат да се наблюдават различни комбинации от очни промени, с различна степенна изява.

Заключение

Описаните в статията ни очни заболявания - изолирани или като част от фенотипа на системна патология, включени в термина „Синдромна глаукома в детска възраст“ са много редки в ежедневната практика на офталмолога, но актуален и значим медико-социален проблем, защото от тях боледува голям брой деца в глобален мащаб, включително у нас, а последиците им засягат живота на боледуващите деца и техните семейства за цял живот. Броят на вече описаните в достъпната литература системни заболявания, асоциирани с глаукома при деца е огромен. Някои от тях са широко известни в света и характерен за болшинството от тях е богат клиничен, етиологичен и клинико-генетичен полиморфизъм, което затруднява ранната им клинична и окончателна диагноза. Кога е началото на глаукомния процес и последващата го патология остава въпрос с все още недоказан отговор. Своевременното доказване на клинико-генетичната диагноза (окончателната диагноза) на вродено детерминираните глаукоми позволява съвременен подход за профилактика на слепотата от глаукома в детска възраст.

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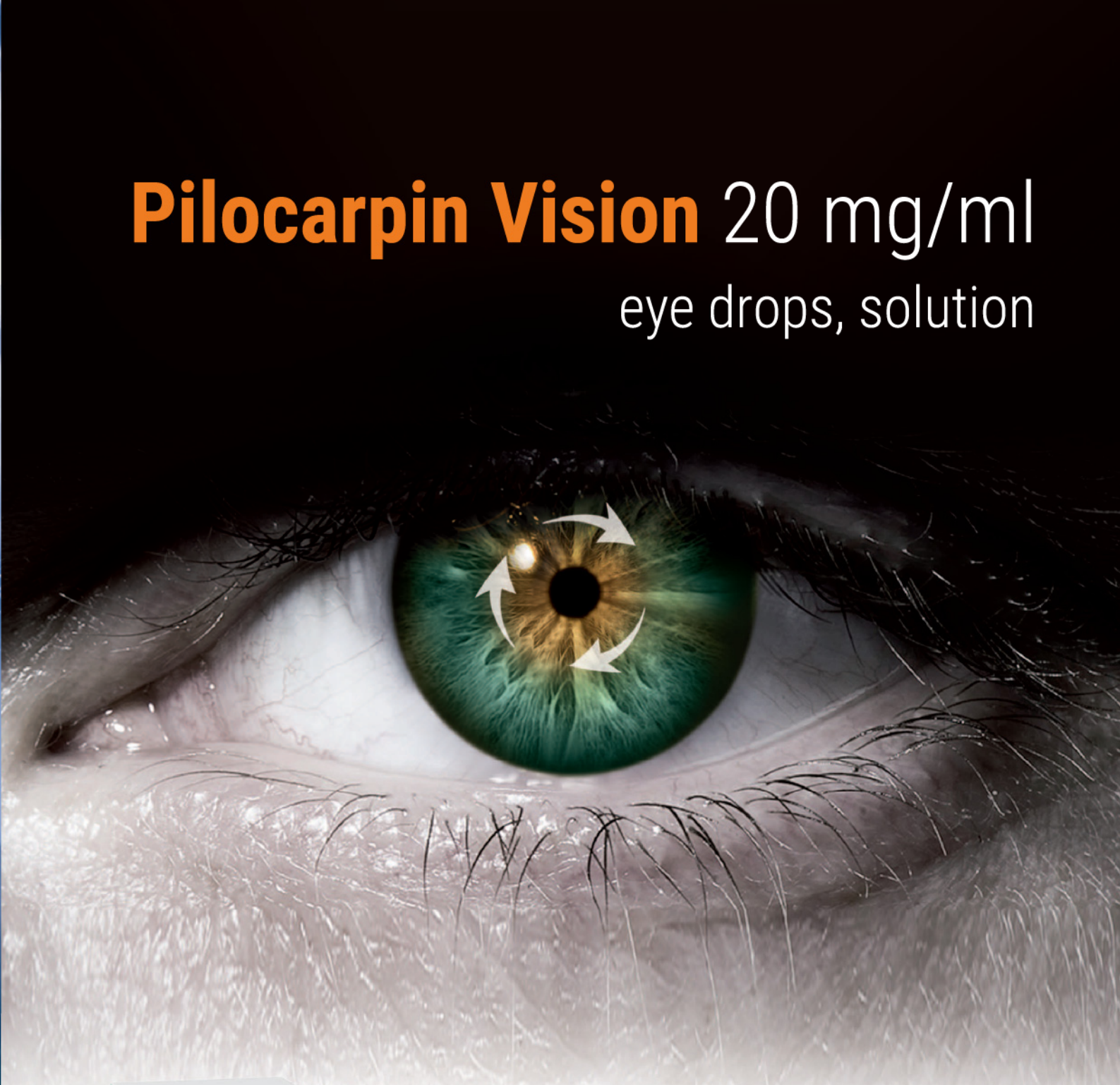

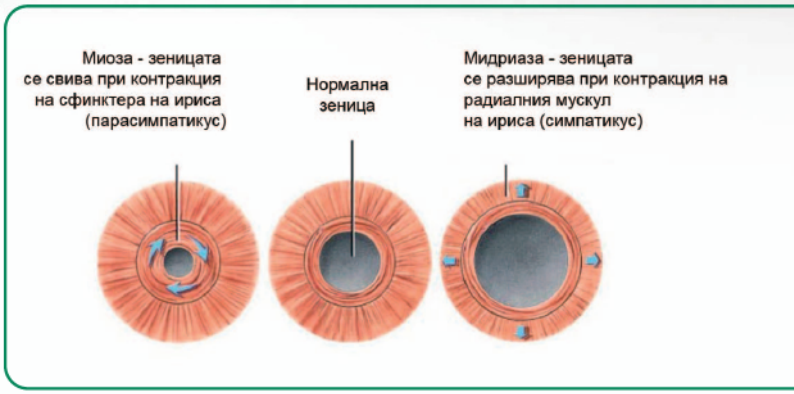

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