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Innovations in glaucoma diagnostics

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ABSTRACT

Glaucoma is the leading cause of irreversible blindness worldwide. It is characterized by progressive loss of retinal ganglion cells and their axons. Glaucoma usually becomes symptomatic only in its severe stages. Therefore, the major challenge to try to prevent visual loss is to identify the disease before it becomes symptomatic. Here we review recent progress in the development of new technologies for detecting and monitoring glaucoma. This review describes most promising findings in tonometry, retinal imaging, visual function testing, electrophysiology and artificial intelligence. The widespread use of new technologies will be useful for clinical diagnosis, prediction of progression and improvement in health care delivery.

KEY WORDS: glaucoma, electrophysiology, tonometry, artificial intelligence, coherence tomography, perimetry.

INTRODUCTION

Glaucoma is a neuropathy affecting the optic nerve, caused by multiple contributing factors, which leads to the deterioration of ganglion cells and their axons, ultimately resulting in damage to the optic nerve and defects in the visual field [1]. Glaucoma occurs in individuals aged 40 to 80 years, with a prevalence rate of approximately 3.4%. It is the main cause of irreversible blindness worldwide. Roughly 76 million people are currently affected by glaucoma, and it is projected that the figure will rise to approximately 112 million by 2040 [2]. Glaucoma presents a significant medical challenge because of its rising incidence, complex pathomechanism that is not yet fully understood, and asymptomatic onset. In the efforts to combat blindness secondary to glaucoma, it is crucial to have effective tools for detecting the disease at its early and asymptomatic stages, and efficient methods for monitoring its progression. This article highlights recent advancements in the technology for diagnosing glaucoma, including imaging techniques, functional tonometry, and artificial intelligence (AI).

TONOMETRY

One of the most crucial risk factors for glaucoma is intraocular pressure (IOP). It is also the only risk factor that can be modified through treatment. Hence, precise measurements and effective management of the IOP are vital both for the diagnosis and monitoring of glaucoma [3]. The most commonly used method is Goldman applanation tonometry (GAT). GAT is based on the Imbert-Fick principle, which states that the pressure inside a sphere equals the force necessary to flatten its surface divided by the area of flattening [1]. While GAT is currently recognized as the "gold standard", it has its drawbacks, including reliance on the examiner's skills, and risk of infection and corneal erosion. Furthermore, GAT requires a slit lamp and needs to be performed on patients in an upright position [4]. Consequently, new instruments for continuous IOP measurement are being developed to enable measurements in the home setting at various times throughout the day. This aspect is particularly important because, according to research, up to 50-75% of IOP spikes occur outside of the opening hours of ophthalmology outpatient clinics [5]. Devices designed for remote IOP measurement can be categorized into two groups: those that directly measure the IOP (placed inside the eye) and those that indirectly assess the IOP through non-invasive methods. Researchers have described IOP sensors integrated with intraocular lens implants [6, 7] and with glaucoma drainage devices such as the Molteno implant [8], and episcleral sensors [9]. In one study, the authors presented a prototype of a wireless device for direct IOP measurements that can be permanently implanted during cataract surgery [10], consisting of a pressure sensor, an RF chip, and antenna, which uses radio waves for wireless power and data transmission. The device, folded into a cross-section

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of 2 mm × 1 mm, is implanted through an incision of 2-3 mm using an injector, and integrated into the capsular tension ring which is routinely implanted during cataract surgery to stabilize the lens [10]. Another permanently implanted IOP measuring device is called the Implandata EyeMate [11]. A microsensor is placed in the ciliary sulcus in front of the lens implant behind the iris during cataract surgery. The technical specifications of the device are as follows: an outer diameter of 11.3 mm, a thickness of 0.9 mm, and a weight of 0.1 g. It is flexible, so it can be folded prior to implantation in the eye. Information is sent to a portable reader via radio waves. The reader must be brought within a range of 5 cm or less from the microsensor. The device has the capability to generate a total of 10 IOP measurements per second. The measurements, when averaged, are displayed on the reader's screen [11]. The Argos study [12] evaluated the measurement accuracy and safety of the Implandata EyeMate device implanted into the ciliary sulcus during cataract surgery in six patients with primary open angle glaucoma (POAG). Four patients experienced a non-infectious inflammatory response in the anterior chamber, which was effectively managed with conservative treatment over a period of 9 days. After one year of follow-up, all patients maintained effective glaucoma control, and their IOP measurements were comparable to those obtained by GAT. At the same time, aside from moderate pupillary distortion and pigment dispersion following the procedure, no significant adverse effects were observed.

Another device (Triggerfish contact lens sensor (CLS), Sensimed AG, Lausanne, Switzerland) is a sensor integrated with contact lenses, designed to measure changes in ocular dimensions across the corneal limbus, thus providing a continuous ocular volumetry monitoring system [13] to identify variations in the biomechanical parameters of the eye throughout the day. Volumetric changes in the eye are thought to correspond to changes in the IOP. A soft silicone contact lens with a diameter of approximately 14.1 mm and a central thickness of 585 μm has a built-in measuring element, a transmitting/receiving antenna, and a microchip. The wireless antenna attached in the periocular area receives a signal from the microchip, simultaneously charging it, and transmits the signal to the portable recorder via a cable [13]. Because of the limited number of *in vivo* studies and high costs, additional research is necessary to evaluate the safety of the mentioned devices and their reliability in comparison to established methods of IOP measurement. However, a practical option for 24-hour IOP measurement for the patient may be an iCare Home autotonometer. ICare HOME is a hand-held tonometer measuring 11 × 8 × 3 cm and weighing 150 g. The device operates on the induction-based rebound measuring principle. An advantage of the device over GAT is that it does not require local anesthesia. ICare HOME also features EyeSmart for automatic eye recognition and EyePos for correct tonometer positioning at the eye. During IOP measurements, the iCare Home is positioned 4-8 mm from the cornea. A single measurement sequence comprises six measurements. The results are saved in the tonometer's memory module and can be viewed on a computer screen or smartphone using dedicated software [14]. Study findings suggest that measurements taken by ophthalmologists with the iCare Home device are similar to those obtained by the patients themselves. Furthermore, measurements taken with the aid of iCare Home show a strong correlation with GAT results, though they may be expected to be slightly lower compared to those obtained by GAT. Also, there is a correlation between the iCare Home measurement results and corneal thickness [14, 15].

EYE FUNDUS IMAGING

Visual assessment of the optic nerve is one of the oldest methods for diagnosing glaucoma. Ocular fundus photography is useful for documenting glaucomatous changes and tracking them over time. The techniques employed in diagnosing glaucoma include color fundus photography, red-free light fundus photography, and stereophotography. Traditional devices offer good quality images, but are large, bulky, cost-inefficient, and require well-trained staff [16]. Advances in technology have led to the miniaturization of fixed cameras with the capability to take photographs of eyes with a narrow pupil, including: 3NETHRA classic [17], and iCare DRSplus [18]. Hand-held digital cameras combined with commercially available optics, such as: Smartscope PRO [19] or PanOptic Ophthalmoscope [20], can be a low-cost, lightweight and easy-to-use alternative to traditional devices. Technological advancements have also sparked a greater interest in the application of smartphones in medicine, giving rise to smartphone-based ophthalmoscopy systems, such as D-Eye system [21] and CelleScope Retina [22]. A comprehensive review of specific models of contemporary devices for fundus photography is presented in the study by Panwar *et al.* [16]. However, further studies are needed to assess the specificity and sensitivity of these new devices in comparison to conventional cameras. Miller *et al.* performed a comparison of the cup-to-disc ratio (CDR) assessment in images captured using a portable 45° non-mydriatic fundus camera (Pictor camera, Volk Optical, Mentor, Ohio) and images taken with a traditional mydriatic camera (Topcon TRC 50 DX, Oakland, New Jersey) in a study group comprising 422 eyes from 211 subjects. The study found no significant difference in CDR measurements between the cameras, and provided evidence that a hand-held non-mydriatic fundus camera could be used to assess the optic disc with an efficacy similar to standard photography [23]. In another study, Swati Upadhyaya *et al.* assessed the sensitivity and specificity of the Smartscope fundus camera (Optomed M5, Oulu, Finland) in evaluating the optic disc for glaucoma [24]. Smartscope is a hand-held, battery-powered non-mydriatic (45°) digital fundus camera weighing only 400 g. It also has an autofocus function, a built-in LED light source, and WiFi connectivity. The study enrolled a total of 68 patients with glaucoma and 70 healthy people. Two investigators remotely assessed fundus photographs of 276 eyes, taken with

a Smartscope camera, in glaucoma screening. The findings were subsequently compared to the results obtained in a wide-pupil examination with a slit-lamp and images captured using a standard fixed 50° Topcon camera (Tokyo, Japan) after mydriasis. The sensitivity of the Smartscope fundus camera compared to the slit-lamp examination was 96.3% and 94.8%, and the specificity 98.5% and 97.8%, for the first and second investigators, respectively. In comparison to the standard camera, the sensitivity was 97.7% and 95.5%, and the specificity was 96.5% and 97.1%, for investigator 1 and 2, respectively [24]. The evaluation of smartphone-based ophthalmoscopy systems is particularly interesting because of their relatively low cost, user-friendliness, video recording capabilities, wide range of available apps, and potential for educational applications. A growing body of research is becoming available on the efficacy of such systems in both screening and remote monitoring – not only in patients with glaucoma but also other conditions like diabetic retinopathy and retinopathy of prematurity [25]. One of such studies was conducted to compare a smartphone-based ophthalmoscopy system in the assessment of the optic disc for glaucoma with the slit-lamp examination [26] and with images obtained from standard cameras [27]. The study found no significant differences between the methods. In another study, fundus photographs taken using Paxos Scope smartphone-based ophthalmic imaging system showed a sensitivity of 67.7% and a specificity of 96.7% in detecting vertical CDR > 0.5 compared to spectral domain optical coherence tomography [28].

In summary, advances in technology have made fundus cameras simpler and easier to use, and therefore more accessible [25]. These features suggest that the new devices could play a major role in glaucoma screening, which is especially important in developing nations and in regions with limited access to ophthalmologists.

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is a non-invasive method for assessing structural damage in glaucoma. At present, it has a very wide range of applications in the diagnosis and monitoring of this disease. Since its introduction to ophthalmology, OCT has undergone major advancements in terms of image quality, imaging protocols, and the incorporation of new parameters. The foundation of OCT analysis is a two-dimensional cross-sectional view of the object under examination, or B-scan, consisting of multiple composite A-scans. First-generation OCT technology (time-domain optical coherence tomography, TD-OCT) had low axial resolution (10-15 μm) and a limited number of A-scans per second [29]. TD-OCT was subsequently replaced by new-generation spectral-domain optical coherence tomography (SD-OCT). Thanks to its improved resolution (3-5 μm) and image quality, and shorter examination time (up to 40,000 A-scans per second), it allows precise and accurate evaluation of the optic nerve head (ONH), peripapillary retinal nerve fiber layer (RNFL) thickness, and ganglion cell complex (GCC) thickness [29]. SD-OCT devices from different manufacturers are available commercially, providing high accuracy not only in tracking the progression of glaucoma but also in evaluating the risk in individuals suspected of having glaucoma. The most recent type of OCT is Swept Source OCT (SS-OCT). SS-OCT relies on longer wavelengths, typically between 1,040 and 1,060 nm, in contrast to SD-OCT (around 840 nm), which improves the visualization of deeper ocular structures, such as the choroid. Furthermore, SS-OCT is characterized by a higher scanning speed, which reduces artifacts and minimizes the effects of optical media opacities on image quality [29, 30]. An additional advantage of SS-OCT is the option to obtain wide-angle scans (9 × 12 mm) encompassing both the optic disc and the macula in a single imaging procedure. In contrast to traditional scans, wide-angle SS-OCT scans enable simultaneous structural imaging of the periocular and macular areas. Consequently, they allow visualization of the continuity of structural changes across these two regions [30]. Studies have provided evidence for good performance of wide-angle SS-OCT in differentiating between eyes with early and preperimetric glaucoma and healthy eyes [31]. In addition, wide-angle SS-OCT was found to be superior to conventional RNFL and GCC assessment in early glaucoma in myopic eyes [32]. Unfortunately, high costs associated with SS-OCT in comparison to SD-OCT currently constrain its widespread adoption in clinical practice [29].

A very promising OCT option for the assessment of microcirculation in glaucoma patients is optical coherence tomography angiography (OCT-A). This non-invasive technology enables imaging of the retinal vessels, choroid, and peripapillary plexuses without the need for intravenous contrast administration. By detecting and measuring the intravascular movement of erythrocytes, and performing numerous scans of the same location, OCT-A identifies blood vessels at various depths. A 6×6 mm scan is most commonly used to detect glaucomatous lesions in the macula, and a 4.5 × 4.5 mm scan is used to identify peripapillary lesions [33]. Parameters used to assess circulation include vessel density (VD), flow index (FI), and blood flow index (BFI) [34]. A large number of OCT-A-based studies evaluating blood circulation in eyes with glaucoma have been published, with findings showing reduced microcirculation in the superficial plexus of the optic disc, peripapillary retina, and macula at different stages of disease progression [34]. In addition, changes revealed by OCT-A are closely correlated with structural modifications of RNFL seen on OCT and defects in the visual field [33]. Furthermore, OCT-A aids in identifying patients who are at risk of rapid glaucoma progression [35].

With the advancement of OCT technology, researchers are also looking for the most effective parameters for diagnosing and detecting glaucoma progression. Ever since the introduction of OCT, researchers have been considering which structures are best to assess, which changes in values are relevant, and how other factors, e.g. age or other

ophthalmic diseases, affect the measured parameters. The optimal indicators for monitoring glaucomatous damage are those providing the most repeatable and objective data. At present, RNFL and GCC are recognized as the most reliable and commonly used OCT parameters. Numerous studies have been conducted to compare the role of RNFL and GCC in the evaluation of glaucoma [36]. However, it is difficult to determine exactly which parameter is the best because of varying sensitivity and specificity of RNFL and GCC at different stages of the disease, as well as limitations in the application of these parameters in other conditions (e.g. GCC in macular disorders, RNFL in developmental disc anomalies, in high myopia). Recently, a new parameter for glaucoma diagnosis has been proposed: Bruch's membrane opening – minimal rim width (BMO-MRW). Bruch's membrane (BM) is a layer separating the choroid from the retinal pigment epithelium. The innermost edge of the BM, known as Bruch's membrane opening (BMO), delineates the border of the optic disc. Research shows that BMO is a more precise indicator in the detection of optic disc boundaries compared to ONH evaluation [37]. In addition, BMO is consistent and repeatable over time, both in healthy and glaucoma-affected eyes. Hence, it has been suggested that BMO might be used as a reference in the assessment of other structures for monitoring glaucoma progression [38]. BMO-MRW is a parameter used for measuring the minimum distance between the termination of Bruch's membrane and the inner limiting membrane (ILM), thus enabling a precise geometric assessment of the neuroretinal rim. BMO-MRW measurement is usually presented as a line perpendicular to the retinal layers and measured at various meridians of the optic nerve disc in radial scans. Research findings suggest that BMO-MRW can be a valuable method for differentiating between healthy and glaucomatous eyes. Changes in BMO-MRW parameters not only precede changes in the visual field, but also exhibit a stronger correlation with these changes, compared to RNFL or ONH. BMO-MRW abnormalities in POAG have been shown to be a sensitive indicator of structural damage and appear earlier than changes in RNFL seen on OCT [39, 40].

ADAPTIVE OPTICS

Adaptive optics (AO) is another promising technique in the diagnosis and monitoring of glaucoma. AO is a technology employed to enhance imaging resolution in optical devices by minimizing optical aberrations [41]. In ophthalmology, optical aberrations occur between the camera and the object being imaged, i.e. the eye, and cause blurring and distortion of the captured image. Unlike previously available technologies, AO eliminates distortion during the examination process, thus improving the lateral resolution of imaging to 2 μm. Initially, adaptive optics was employed in astronomical telescopes to reduce the effects of the Earth's atmospheric distortion [1, 41]. Thus, AO represents a unique technology that enhances imaging quality and assessment of ocular structures at the cellular level *in vivo*, such as individual photoreceptors or blood vessels [42]. Importantly, AO does not create images itself, but is built into other optical devices [1]. At present, nearly all optical devices used in ophthalmology are equipped with AO capabilities, for example adaptive optics fundus cameras (AO-FC), adaptive optics optical coherence tomography (AO-OCT) devices, and adaptive optics scanning laser ophthalmoscopes (AO-SLO) [42]. AO technology has found wide applications in structural imaging, e.g. in retinal dystrophies, age-related macular degeneration, diabetic retinopathy, myopia, and glaucoma [41]. Adaptive optics is the only technology that allows the imaging and measurement of a single bundle of nerve fibers *in vivo* [43]. Furthermore, AO-SLO revealed a link between the width of nerve fiber bundles and impaired visual field sensitivity, along with a correlation between bundle width and RNFL thickness in glaucomatous eyes [44]. Using AO, numerous authors have studied the density and distribution of photoreceptors in both healthy eyes and in patients with various diseases [41]. Several AO-based studies assessing cones in glaucoma have also been published. However, the study findings are contradictory. In one study utilizing AO-FC, the authors identified dark regions within the mosaic of cones in retinal areas with compromised visual field sensitivity in glaucomatous eyes. The dark areas were found to expand in size as the severity of changes in visual field increased [45]. Nonetheless, another study failed to show any effects of glaucomatous lesions on the cone layer [46]. AO allows accurate assessment of vessel diameter, vessel wall thickness, and vessel lumen diameter. Hugo *et al*. evaluated the superior temporal arteries using AO-FC in patients with glaucoma and in the control group. The study showed a significant decrease in the arterial diameters and arterial lumen diameters among glaucoma patients in comparison to the control subjects [47]. Imaging techniques in conjunction with adaptive optics (AO) also enable precise, previously unattainable, *in vivo* imaging of the lamina cribrosa [48] and trabecular meshwork [49] at the microscopic level.

PERIMETRY

Perimetry, or examination of the visual field, remains one of the most important techniques in the diagnosis and monitoring of glaucoma. Even though perimetry has been used in ophthalmology for many years, detecting the progression of changes in the visual field and identifying early glaucomatous defects remain a challenge. Standard automated perimetry (SAP) is fundamental in the diagnosis of functional optic nerve damage. SAP determines the threshold sensitivity of the retina (expressed in dB) at different points in the visual field by presenting stimuli with varying brightness. The most commonly used automatic perimeters are the Humphrey Field Analyzer (HFA) and Octopus [1]. However, accurate interpretation of perimetric results requires high-quality examination. The difficulty involved in SAP is that the subjects must keep their gaze

fixed on the target throughout the examination. The quality of SAP examinations may also be influenced by a range of psychological factors, including attention level, stress, and experience, as well as ophthalmic aspects, such as reduced optical transparency or dry eye syndrome. Research has demonstrated that false-negative errors can lead to worse results, false-positive errors can yield improved results, while loss of fixation can cause incorrect location of the blind spot. Notably, fixation instability is observed even in well-trained subjects [50]. An interesting solution to this issue has emerged with the advancement of a perimetry technique known as fundus-tracked visual field testing. The COMPASS device (CenterVue, Padova, Italy), introduced in 2014, employs continuous retinal imaging and active dislocation of stimuli to allow precise stimulus presentation in specific retinal locations, independently of the patient's fixation [51]. Compass consists of a perimeter, a scanning ophthalmoscope, a fundus tracker, and a tablet to operate the system. The device utilizes perimetric functions similar to SAP HFA, and enables assessment of the visual field within the central 10 degrees, and 24 and 30 degrees. The added feature of color wide-angle 60 degrees × 60 degrees fundus photographs allows the integration of techniques for evaluating structural and functional changes in a single device [51]. Another example of linking structural and functional methods is the Combined Structure Function Index (CSFI), which is calculated on the basis of a combination of SAP and OCT results [52].

Advancements in perimetry include the development of novel perimetric algorithms and the application of improved analytical methods to detect progression, enhance test sensitivity, and shorten the duration of assessment. The frequency of the examination is an important factor in tracking the progression of visual field loss [53]. As the examination frequency increases, the time required to detect statistically significant progression of changes in the visual field decreases. Wu Z *et al*. found that 80% of eyes with an MD deterioration of –2 dB/year would be diagnosed after 3.3, 2.4 and 2.1 years if examination is performed once, twice and three times per year, respectively [54]. Consequently, providing opportunities for regular and frequent examinations is of utmost importance for patients, and the emergence of various innovative remote perimetry technologies contributes to this goal. One of the most promising devices is the Melbourne Rapid Fields (MRF) (GLANCE Optical Pty Ltd, Melbourne, Australia). MRF is an iPad app designed for perimetric examinations to assess both central and peripheral visual fields. The app automatically adjusts the required screen brightness, tracks the patient's fixation, and delivers voice messages. The testing range comprises a total of 66 test points covering horizontally 34° and vertically 25° of the visual field. The examination takes approximately 4 to 6 minutes to be performed [55]. MRF employs operating methods that are similar to HFA, and also evaluates MD and PD, and detects false positives and false negatives. Studies comparing HFA 24-2 with MRF showed that MD and PD measurements performed by MRF were in agreement with HFA results, and the repeatability of MRF examinations was similar to the traditional SAP HFA assessment. However, a higher rate of fixation loss was observed in MRF compared to HFA examinations [56]. Another interesting technology designed for home-based perimetry is the IMO (CREWT Medical Systems, Tokyo, Japan) – a portable head-mounted perimeter that does not require a dark room and can be used by patients in any body position. The results obtained with the IMO device correlate well with SAP HFA results [57]. Other examples of remote perimetry include the visual fields easy (VFE) app, which is available on the iPad platform, and the new computer-based software called the Moorfields Motion Displacement Test (MMDT) [58].

ELECTROPHYSIOLOGY

As mentioned above, early detection of glaucoma is one of the greatest challenges in ophthalmology due to the complex underlying pathomechanism of the condition and the fact that structural damage often precedes functional changes. Electrophysiological assessment of the visual system has the potential to complement traditional evaluation methods and improve the early detection of glaucomatous lesions [59]. At present, the following methods are recommended for glaucoma diagnosis: pattern electroretinogram (PERG), photopic negative response (PhNR), visual evoked potentials (VEP), and multifocal visual evoked potentials (mfVEP) [59]. PERG is the retinal response to a black-and-white checkerboard stimulus. The response consists of N35, P50, and N95 waves. The initial wave, N35, is marked by considerable variability and is not considered clinically significant. The constant waves are the P50 wave, which mainly reflects the function of the macula, and the N95 wave, which depends on the functioning of retinal ganglion cells (RGCs) [60]. Research has validated that PERG correlates well with RGC loss and RNFL thinning in glaucoma, and helps with the assessment of the risk of glaucomatous damage in eyes with ocular hypertension [59, 61]. However, the PERG result is a cumulative response and depends on various factors, which is why changes indicative of glaucomatous damage are non-specific and difficult to determine. Hassankarimi H. used discrete wavelet transform (DWT) for the purpose of quantifying the PERG responses more accurately. DWT is a method designed to analyze and process raw signals used in various applications, including electromyography (EMG) and electroencephalography (EEG). In the study, DWT yielded PERG responses that were more precise and consistent, and allowed better differentiation between glaucomatous abnormalities and normal results, when compared to the standard test [62]. Salgrello *et al*. found that PERG exhibited good accuracy in detecting localized visual field defects. The finding could be particularly valuable in cognitively impaired patients or young children in whom it may be difficult to conduct perimetry tests accurately [63]. Another interesting application of PERG

in glaucoma was reported by Karaśkiewicz *et al*. [64]. In patients diagnosed with early-onset glaucoma who had not yet received treatment, the function of RGCs was evaluated by PERG both before and after the initiation of IOP-lowering therapy. The study showed that following an IOP reduction of approximately 31%, an increase in the P50 (average 28%) and N95 (average 38%) wave amplitude was achieved in 75% and 79% of eyes, respectively [64].

Another method, known as photopic negative response (PhNR), relies on retinal ganglion cells and their axons, much like PERG. However, unlike PERG, PhNR is not affected by refraction or disruptions in the transparency of the optical media. PhNR takes the form of a slow negative ERG wave following a positive b-wave under photopic conditions [59]. Machida *et al*. showed that PhNR correlated with the severity of morphological and functional changes in glaucoma [65]. Also, Cvenkel *et al*. demonstrated that a decrease in PhNR amplitude in eyes suspected of glaucoma is linked to alterations in peripapillary retinal and macular thickness. On that basis, the authors argued that PhNR could serve as a sensitive test for early-stage glaucoma [66].

A visual evoked potential (VEP) examination is widely used in various optic nerve diseases. It also reveals abnormal findings associated with glaucoma, such as delays and/or reduced amplitudes. However, since VEP reflects the function of the entire visual pathway, the test is not inherently specific. To increase the diagnostic value of VEP in glaucoma, special techniques have been developed, including short duration transient VEP (SD-tVEP) and isolated-check VEPs (ic-VEPs) [61]. To determine the diagnostic value of these new methods, studies comparing them with SAP and OCT are conducted [59]. It is notable to mention multifocal mfVEP, which can be used as a type of objective perimetry. MfVEP involves simultaneous spatial recording of multiple local VEP responses, which makes it possible to pinpoint glaucomatous lesions. This is particularly important in poorly cooperative patients, who have difficulties in conducting perimetry [67]. Research findings show a good correlation between retinal sensitivity in the visual field and mfVEP results [68]. However, mfVEP also has a range of limitations. In addition to being time-intensive, it needs thorough preparation, and an electrophysiology laboratory must be available to conduct the examination.

Recently, Nakanishi *et al*. introduced the nGoggle system (nGoggle Inc, San Diego, California), which is a portable Brain-Computer Interface (BCI) method capable of effectively analyzing electrical brain signals, similarly to VEP [69]. BCI uses multifocal steady-state visual evoked potentials (mSSVEPs) triggered by rapid flickering stimulation. Compared to the standard mfVEP technique, BCI is quicker to perform and less susceptible to artifacts. In a study evaluating the diagnostic efficacy of BCI, it was found that the system was capable of differentiating between the eyes with glaucomatous damage and healthy eyes [69]. While additional research comparing the obtained results to the standard methods is needed, BCI shows promise as a method of objective remote assessment of functional changes in glaucoma.

ARTIFICIAL INTELLIGENCE

Rapid advancements in technology have led to an increasing integration of technological solutions into everyday medical practice. Artificial intelligence (AI) and its applications in the field of medicine have generated a considerable interest worldwide. AI was first described in 1956 as a technology designed to mimic the human 'cognitive' functions [70]. AI involves the processing of vast amounts of data using rapid algorithms to carry out tasks that are traditionally associated with human intelligence, such as decision-making or the identification of specific characteristics. One of the branches of AI is Deep Learning (DL), which relies on the development of multi-layer neural networks that enable machines to learn through the processing of their own data [71]. The past decade has witnessed a rapid expansion of the applications of AI within the field of ophthalmology, e.g. in the diagnosis of various conditions including diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, and glaucoma [71]. In glaucoma, DL is employed for evaluating structural alterations (such as fundus photographs and OCT) as well as functional changes (perimetry) in screening, diagnosis of early glaucomatous defects, and detection of disease progression. Studies found DL to be highly sensitive and specific in optic disc assessment for glaucoma-associated changes on color fundus photographs [72]. In studies assessing RNFL and GCC thickness on OCT, DL also showed promise in the early diagnosis of glaucoma [73]. Furthermore, the usefulness of AI in detecting early visual field defects and their progression has been confirmed [74]. Another interesting potential application of AI is the assessment of prognosis in glaucoma patients. For example, Kazemian *et al*. developed a system predicting what progression can be expected in patients with POAG at different IOP levels. The system can assist users in making more informed and individualized decisions about the intensity of anti-glaucoma treatment and the target IOP level in a given patient [75]. A simple and cost-effective glaucoma screening platform based on DL algorithms was developed by Żmijewska *et al*. The platform has the capability to identify glaucomatous neuropathy through the analysis of color fundus photographs and non-contact IOP measurements. The platform makes use of classifiers that autonomously evaluate the parameters listed above: the fundus image classifier relies on mathematical models, while the IOP classifier is based on predefined thresholds. Studies evaluating the sensitivity and specificity of the platform have demonstrated its functionality and effectiveness in differentiating between healthy individuals and patients with glaucoma in real-world screening scenarios [76]. Another solution, named GlaucomAI IDSS System, was proposed by Wasilewicz *et al*. It is the first

intelligent system that does not use the IOP as its attribute and allows differentiating between eyes affected by glaucomatous neuropathy, neuropathy-free eyes, and eyes affected by non-glaucomatous neuropathy. GlaucomAI describes the interactions between the volumetric parameters of the eye and the functional parameters of the cardiovascular system. Based on this data, the system employs machine learning algorithms to build a predictive model for the progression of neuropathy, which facilitates therapeutic decisions and makes it possible to tailor anti-glaucoma treatments to individual patients [77, 78].

CONCLUSIONS

Even though there are multiple clinically established diagnostic methods for glaucoma, there remains a significant demand for new instruments to identify early glaucomatous changes and track their progression with a view to improving disease management. Recent advancements in the assessment of structural and functional glaucomatous changes hold significant promise. However, before the new methods are adopted on a wider scale, they need additional evaluation focused on sensitivity, specificity, repeatability, and cost-effectiveness.

DISCLOSURE

The authors declare no conflict of interest.

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