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Objective Measures of Visual Function in Papilledema

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Synopsis

Visual function is an important parameter to consider when managing patients with papilledema. Though the current standard of care uses standard automated perimetry (SAP) to obtain this information, this test is inherently subjective and prone to patient errors. Objective visual function tests including the visual evoked potential, pattern electroretinogram, photopic negative response of the full field electroretinogram, and pupillary light response have the potential to replace or supplement subjective visual function tests in papilledema management. This article reviews the evidence for use of objective visual function tests to assess visual function in papilledema and discusses future investigations needed to develop them as clinically practical and useful measures for this purpose.

Keywords

papilledema; optic nerve; retinal ganglion cells; visual evoked potential; electroretinogram; photopic negative response; pupillary light response

INTRODUCTION

Papilledema is swelling of optic nerve head that occurs as a consequence of elevated cerebral spinal fluid (CSF) pressure in the optic nerve sheath compressing the retinal ganglion cells (RGCs) that form the optic nerve and the blood vessels that supply them.^{1,2} Any cause of elevated intracranial pressure (ICP) can cause papilledema, including brain tumors, venous sinus thrombosis, meningitis, and idiopathic intracranial hypertension (IIH). Irreversible blindness due to RGC injury is a devastating consequence of papilledema, occurring in 6–14% of patients with IIH, with 50% suffering some degree of vision loss.^{3,4} Treatments are aimed at reducing CSF pressure on the optic nerve either directly through optic nerve sheath fenestration, or indirectly by reducing intracranial CSF production through medication or by draining CSF from the cerebral ventricles or spinal canal. These treatments are effective for reversal or stabilization of vision loss from papilledema and

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sometimes are needed in addition to directed treatment aimed at the underlying cause of ICP elevation.⁵

Visual function measurement, using standard automated perimetry (SAP), for example, using the Humphrey Visual Field Analyzer (Zeiss Meditech Inc) is a primary basis for papilledema management decisions because it assesses the clinical outcome of interest.⁶ However, as a psychophysical test, SAP is inherently subjective and prone to patient error. This introduces uncertainty into interpretation of its results with respect to RGC function.⁷ Objective measures that accurately assess the function of the injured neurons could serve as an alternative or additional clinical marker upon which to base treatment decisions. Identifying and characterizing these measures are of significant importance to the ophthalmology and neurology communities who are striving to improve clinical care of IIH and prevent vision loss from papilledema. A recent example of these efforts is the IIH treatment trial (IIHTT), which was sponsored by the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) and National Eye Institute (NEI).^{5,8}

In addition to overcoming the limitations of SAP, objective measures of visual function have the potential to provide information not currently captured by SAP by representing physiological responses beyond those contributing to conscious visual function. Literature regarding other optic neuropathies suggests that objective visual function measures are more sensitive than SAP because abnormalities on some objective measures of visual function based on electrophysiology may precede vision loss as measured by SAP.⁹ This could facilitate earlier identification of visual dysfunction or its progression. Furthermore, objective measures of visual function may capture predictive or prognostic information that SAP does not. This article reviews methodologies for objective measurement of retinal ganglion cell function and evidence of their applicability for assessment of visual function in papilledema.

SIGNIFICANCE

Basis of objective visual function measurements

All measurements of vision aim to determine a person's ability to perceive a certain light stimulus. Stimuli range from a brief flash of light, as is the case in full field electroretinography (ERG) to formed images of standard sizes, as is the case in Snellen visual acuity testing. For psychophysical measurements, such as visual acuity or perimetry, a patient indicates the presence or absence of perception either verbally or through another conscious action such as pushing a button. In contrast, objective measurements do not ask for a conscious response from the patient, rather they collect physiological measurements from which information regarding function of part or parts of the visual pathway is/are extracted. The most common physiological measurement is an electrical signal, for example from the retina (ERG) or visual cortex (visual evoked potential (VEP)). Other measureable signals include change in pupil size, for example in the pupillary light response, or nystagmus, for example in optokinetic nystagmus (Table 1).

Electrophysiological and pupil based measures of RGC function offer advantages over SAP because they are objective, and have minimal patient demands. They are appropriate to

consider as clinical markers because they are quick and non-invasive. There are multiple tests relating to RGC function that are abnormal when RGCs are compromised, including the visual evoked potential (VEP), pattern electroretinogram (PERG), photopic negative response (PhNR) of the full field electroretinogram (FF-ERG), and pupillary light response (PLR). These vary in their requirements for refraction, dilation, fixation, and maintaining open eyes. They also vary in the anatomical specificity of the physiological signal they measure (Table 2).

Visual Evoked Potential (VEP)

The visual evoked potential is a waveform recorded by electrodes placed over the skin overlying the occipital lobe in response to a controlled visual stimulus. The most commonly used stimulus is “pattern reversal” consisting of an alternating black and white checkerboard pattern in the central/mid visual field. Less often used stimuli include pattern onset, pattern offset, and flash, which have more variability between individuals. The measured signal is an electrical potential as a function of time with latency and amplitude of the first positive peak (p100) being the primary outcome measure of the transient response or phase and amplitude in the steady state response. Due to the type of stimulus and the placement of recording electrodes the signal mainly captures the function related to the central area of the visual field. The signal can be altered by pathology anywhere along the visual pathway including retina, optic nerve and hemispheric causes of visual impairment. Stimulus factors that affect the VEP include the spatial frequency of the stimulus (i.e. the size of the checks), the total size of the stimulus visual field, and the temporal frequency of the stimulus (i.e. speed of the stimulus change). Low frequency stimuli capture the transient response, while high frequency stimuli capture the steady state response. Subject factors that affect the VEP include age and refraction. The subject must maintain fixation on the center of the stimulus field for the duration of the test. Therefore refractive correction, subject attention, and subject effort are necessary for high quality measurements.¹⁰

The most common VEP abnormality reported in association with papilledema is prolonged p100 latency (transient response) or delayed phase (steady state response)(Table 3).^{11–17} Estimates of the prevalence of prolonged VEP latency in IIH, a disease characterized by papilledema, ranges from 10–55%, with only some studies demonstrating a significant difference between IIH and control groups. One study of children with craniosynostosis, another disease associated with elevated ICP and papilledema, reported normal latency in all 5 patients with papilledema.¹⁸ Multiple studies have evaluated VEP longitudinally, uniformly reporting shortening of latency following treatment of ICP.^{11,13,14,19} One study included a single patient with progressive vision loss due to papilledema; this was associated with progressive latency delay.¹²

VEP amplitude abnormalities were not found by most investigators between IIH and control subjects. Falsini et al reported the association between VEP amplitude and stimulus spatial frequency to be different in IIH and control subjects with IIH subjects having decrease of normalized amplitudes with high spatial frequency stimuli, while control subjects had decrease of amplitudes with low spatial frequency stimuli.²⁰ Liasis et al reported progressive

amplitude decrease prior to ICP lowering surgery in craniosynostosis in 8 patients and recovery following operative intervention to lower ICP in all of them.¹⁸

One possibility for the low prevalence of abnormalities is that papilledema pathology may affect the VEP less than other optic nerve diseases. This was suggested by one study that demonstrated VEP abnormalities in IIH to be less prevalent than in other optic neuropathies (e.g. optic neuritis, thyroid eye disease) with similarly mild degrees of vision loss.¹⁵ This low sensitivity of VEP abnormalities for papilledema was also demonstrated by Verplanck et al who found only 5/30 eyes in their study to have abnormal VEP, despite 18 eyes and 15 eyes demonstrating abnormal contrast sensitivity or visual fields respectively.¹⁶ Similarly Kesler et al reported that only 4/10 eyes with abnormal visual fields had abnormal VEP.¹⁷ One study found pattern ERG to be more sensitive for papilledema detection than VEP.²⁰

It is important to keep in mind that VEP interrogates the entire visual system, not just the optic nerve that is structurally affected by papilledema. Some studies present evidence that elevated ICP may affect VEP through effects on intracerebral structures other than the optic nerve. Onofrj et al demonstrated VEP latency delays in patients with hydrocephalus without papilledema, and proposed that there may be an intracranial effect of elevated ICP on the VEP, perhaps through effect on the optic radiations.²¹ One of their subjects who had both hydrocephalus and papilledema had improvement in VEP latency rapidly following CSF shunting procedure prior to resolution of papilledema. Mursch et al also contribute evidence for central visual pathway contributions to abnormal VEP with their observation of delayed VEP in 12/52 children with craniosynostosis, none of whom had papilledema, and only one of whom had optic atrophy.¹⁹

Multifocal VEP is a newer test that measures spatial variation in the VEP signal to create a 2 dimensional VEP map. This is achieved by using a time varying complex signal pattern and complex signal analysis. It has been shown to correlate with visual field defects in other optic neuropathies.^{22,23} However, a literature review did not locate studies using this technique in papilledema.

Full Field Electroretinography (FF-ERG) and the Photopic Negative Response (PhNR)

The full field electroretinogram is a waveform recorded by electrodes in contact with the cornea (preferred) or skin adjacent to the eye in response to a flash or flicker of light occupying the entire visual field and thus stimulating the entire retina. Pharmacological pupillary dilation is typically used to maximize exposure. Stimulus parameters such as color, luminance, and duration can be manipulated in light or dark adapted conditions to generate or accentuate components of the waveform that localize to specific components of the retinal circuitry.²⁴ The International Society for Clinical Electrophysiology in Vision (ISCEV) has established standards for clinical FF-ERG recordings including technique and minimum stimuli to be administered.²⁵ The measured parameters are the amplitude and timing (implicit time) of peaks in the waveform (a, b) and high frequency components (oscillatory potentials). Due to the diffuse and brief nature of the stimulus, demands on the subject to fixate are minimal. Refractive correction is not needed, though people with high myopia tend to have smaller signals, likely due to increased distance between the electrode and the retina.

Of particular interest with respect to papilledema is the photopic negative response (PhNR), which is the negative wave following the b wave, the main positive wave of the full field ERG. The amplitude of the PhNR is reduced in other optic neuropathies, including glaucoma and optic atrophy. Animal studies and structure function correlations provide additional evidence that it is generated by the RGCs^{26–29}. Though discernable on ISCEV standard recordings, studies focusing on the PhNR typically use specialized protocols consisting of a red flash on a blue background, because these accentuate the PhNR.³⁰

In a study of 10 IIH patients with variable papilledema grades, PhNR was reduced compared with controls, and 6/10 IIH patients had abnormal PhNR outside of the range of control measurements (Table 4).³¹ Log PhNR was linearly associated with a subjective test of visual function, SAP. Log PhNR was highly correlated with ganglion cell atrophy and papilledema severity, both structural measures of ganglion cell changes. In one subject with high-grade papilledema and minimal visual field loss, PhNR was absent and recovered with treatment of ICP and resolution of papilledema.

Waveforms of the full field ERG other than the PhNR have not been widely studied in papilledema, likely because they represent retinal structures of which there is unlikely to be dysfunction associated with papilledema. However, a single study reported prolonged latency of the scotopic and photopic responses to low and high frequency flicker respectively in two patients with papilledema (Table 4). Both patients had normalization of ERG latency and papilledema following surgical intervention.¹¹ The manuscript indicates similar findings in 6 other patients with papilledema. The mechanism of this puzzling observation was not elucidated, though the authors proposed outer retinal dysfunction related to transsynaptic signaling or metabolic disturbance related to hemodynamic changes.

Similar to multifocal VEP, multifocal ERG measures spatial variation of the ERG within the central visual field.²⁴ It is much more sensitive to changes in the macula than the full field ERG. Changes have been demonstrated in glaucomatous eyes, but, to our knowledge, it has not been applied to papilledema.³²

Pattern Electrophoretography (PERG)

The pattern electrophoretogram (PERG) is a waveform recorded by electrodes in contact with the cornea in response to a pattern reversal stimulus in the central visual field. Spatial and temporal frequency can be manipulated and there are ISCEV standards for clinical testing.³³ Unlike FF-ERG, pupillary dilation is not required. Similar to pattern reversal VEP, refractive correction is required and the subject must maintain visual fixation on the stimulus. The measured parameters are the amplitudes of the P50 and N95 peaks of the PERG waveform and the N95:P50 ratio. Evidence suggests that RGCs contribute partially to P50 and are the predominant contributor to N95. Due to the small size of the signal, responses to repetitive stimuli must be averaged. Subject fixation with minimal blinking is essential to achieve this.³⁴

Studies have measured PERG in mild active papilledema with minimal or no visual field loss²⁰ and in post-papilledema atrophy with visual field loss (Table 4).³⁵ Both found reduced amplitudes to be associated with papilledema. However spatial frequency effects were

opposite, with the group that studied mild active papilledema demonstrating more normalized amplitude decrement at higher spatial frequencies (smaller stimulus size), while the group that studied post papilledema atrophy demonstrated a more prominent effect at the lower spatial frequency (larger stimulus size). In one study, PERG detected abnormalities in a higher proportion of subjects than VEP, suggesting that it is more sensitive for detection of papilledema pathology.²⁰ In the other study correlations between PERG and both visual field loss and structural loss of RGCs were demonstrated.³⁵

Pupillary Light Response (PLR)

The pupillary light response is a measure of the change in pupil size in response to light stimulation.^{36–38} By varying the light color (wavelength), light intensity, and eye adaptation, it is possible to characterize components of the pupillary light response driven by rod, cone, and melanopsin ganglion cell pathways. Rod and cone pathway responses are measured by the amplitude of the transient pupillary constriction, often normalized to baseline size. Melanopsin ganglion cells are intrinsically photosensitive and do not contribute to conscious visual perception. Their pupil response has a characteristic slow recovery measured as the sustained response. The PLR response has been studied and is abnormal in other early optic neuropathies including glaucomatous, compressive, and ischemic.³⁶

IIH patients demonstrate abnormalities in all components of the PLR, with the sustained melanopsin response demonstrating the largest area under the curve in receiver operating characteristic analysis against control subjects (Table 4).³⁹ The amplitude of the sustained (melanopsin) PLR is correlated with SAP, a subjective measure of visual function and log PhNR, another objective measure of visual function in IIH patients.

CURRENT CLINICAL RELEVANCE

Current clinical use of objective measures of visual function in papilledema mostly consists of VEP, the most widely available electrophysiological test, in cases where there is concern for malingering or somatoform disorder causing false positive subjective visual function testing. VEP has likely not been applied more broadly in papilledema management due to lack of evidence that VEP exceeds subjective visual function testing as a sensitive and specific marker of visual dysfunction associated with papilledema. Subjective visual function testing is also more widely available and less technically challenging. PERG, PhNR, and PLR have not been sufficiently studied in the papilledema and IIH populations to justify widespread clinical adoption. Furthermore, the technical requirements current limit the availability of testing to centers with expertise in electrophysiology.

Future avenues for investigation

The next step to develop PERG, PhNR, and PLR for clinical application in papilledema management is to characterize the responses in terms of associations with other disease markers, variability, and reliability. This will require large-scale studies of populations in whom these measures might be used as clinical markers, for example, patients with IIH and control subjects. Longitudinal studies are necessary to fully understand how the

measurements change within individuals over time and how measurements relate to concurrent standard visual markers and future disease course. These studies will also refine how objective visual function markers might most contribute to clinical care of papilledema.

It will next be important to determine if objective visual function testing improves clinical care. This should be considered in a broad sense. Clinical care could be improved by improving visual outcomes or by reducing health care expenditures or by facilitating new patterns of care. For example, if objective visual outcome measures are easy to administer and interpret for a non-expert, they might be of use in the emergency room setting where ophthalmic expertise is not readily available.

Published studies applying PERG, PhNR and PLR have used careful methodology, requiring expertise and equipment that is impractical for wide scale clinical implementation. This will limit broad adoption, even if the data gained from the other proposed experiments supports widespread use. Development of testing platforms that are less operator dependent and less expensive will enhance feasibility of clinical use.

Summary/Discussion

Objective measures of visual function address many of the shortcomings of subjective visual function measures. The visual evoked potential, full field electroretinogram, pattern electroretinogram, and pupillary light response all have demonstrated abnormalities in association with papilledema. Though VEP has been investigated most widely, studies suggest that it is less sensitive to visual function change in papilledema than subjective visual function testing. PERG, PhNR of the FF-ERG, and PLR show more promise as new or additional clinical markers for papilledema due to higher sensitivity and correlation with other markers of papilledema. PERG, PhNR of the FF-ERG, and PLR are all associated with subjective measures of visual function in IIH, suggesting that they are an index of the outcome of interest (i.e., visual function). PhNR and PERG have been shown to be associated with structural measures of ganglion cell abnormality in IIH, supporting its development as a marker of ganglion cell function in IIH. Other potentially interesting measures, namely multifocal VEP and multifocal ERG have not been investigated in the papilledema population.

Objective measures of visual function, in particular PERG, PhNR and PLR have important potential application to the diagnosis and management of IIH either as a replacement for subjective visual function testing or as a supplementary test in addition to subjective measures of visual function. They need not be a perfect test to have clinical utility. For example, if they can be shown to have high specificity for visual pathway compromise associated with papilledema, their results would help to exclude visual dysfunction and avoid overtreatment. Alternatively, if they can be shown to have high sensitivity for visual pathway compromise associated with papilledema, their results would help to screen for visual dysfunction and identify those who might be in need of further testing and/or care. If they provide additional diagnostic or prognostic information beyond what is captured by subjective visual function testing, their results may provide additional information to physicians to guide management of papilledema. While published data suggest that PERG, PhNR, and PLR are promising with respect to these applications, substantial additional

investigation is necessary to develop them to the level of widespread clinical implementation in the area of papilledema diagnosis and management.

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Key Points

1. Though the visual evoked potential has been widely studied in papilledema, its sensitivity for vision loss is less than standard subjective visual function tests.
2. The photopic negative response of the full field electroretinogram is abnormal and associated with ganglion cell atrophy and papilledema grade in patients with idiopathic intracranial hypertension.
3. The pattern electroretinogram is abnormal and correlated with ganglion cell loss in post papilledema subjects with stable vision loss.
4. The sustained pupillary light response is abnormal in patients with idiopathic intracranial hypertension and correlates with subjective and other objective measures of visual function.
5. Further investigation is needed to characterize changes in objective visual function tests in papilledema to develop them into clinically useful diagnostic tests for this disease.

Table 1

Comparison of subjective and objectives measures of visual function

	Subjective	Objective
Examples	Snellen visual acuity Perimetry (automated or manual; static or kinetic)	Visual evoked potential Electroretinogram Pupillometry
Typical stimulus	complex lines (e.g. letters) light stimuli in varying locations	full field light time varying graphical pattern
Response	Subjective by the patient (e.g. verbal or button pressing)	Electrical or imaging waveform
What test is measuring	Integrated function of visual system	Physiologic response of sections of the visual system
Causes of underestimation (false negative)	Poor subject cooperation (voluntary * or otherwise) Incorrect testing protocol	Poor signal recorded Incorrect testing protocol

* e.g. malingering, factitious disorder

Table 2

Comparison of objective measures of retinal ganglion cell function

	Visual evoked potential	Full field electroretinogram	Pattern electroretinogram	Pupillary Light Response
Standard stimulus	Pattern reversal: Alternating black/white checkerboard pattern in central visual field	Full field brief flashes of light in DA or LA state	Pattern reversal: Alternating black/white checkerboard pattern in central visual field	Full field brief flashes of light
Specialized stimuli	Sinusoidal pattern reversal Pattern onset Pattern offset Full field flash	PhNR: Blue light flash on red background, LA		Melanopsin: bright blue light, DA Cone: Red light, LA Rod: dim blue light, DA
Recording location	Skin over occiput	Cornea	Cornea	Infra-red image of pupil recorded with camera
Subject Requirements	Maintain open eye Maintain Fixation Refractive correction	Maintain open eye Dilated pupil	Maintain open eye Maintain fixation Refracted correction	Maintain open eye
Structures assessed	Entire visual pathway	Eye, retina	Eye, retina	Eye, optic nerve, brainstem
Output	electroencephalogram	Electroretinogram	Electroretinogram	pupil size
Measures relevant to RGC function	P100 latency & amplitude	PhNR amplitude	N95:P50 amplitude ratio	Magnitude of transient response Magnitude of sustained response

DA – dark adapted, LA – light adapted, PhNR – photopic negative response, RGC – retinal ganglion cell, P100 – positive peak at approximated 100ms, P50 – positive peak at approximately 50ms, N75 negative peak at approximately 75ms

Table 3

Studies reporting visual evoked potential (VEP) results in subjects with papilledema (in chronological order, * indicates statistically significant finding)

Recording/ study	stimulus	n	Papilledema subject details	comparison	findings	Correlation with other measures	Follow up
VEP							
Kirkham, 1981 ¹¹	Full field flicker (steady state)	2	brain tumor with papilledema (n=2)	Lab norms	Latency delayed (LA) Latency normal (DA)	ERG latency prolonged (LA, DA) (see table 4)	Latency normalized with ICP improvement
Onofri, 1981 ²¹	Pattern reversal (sinusoidal pattern, 2 temporal frequencies)	6	papilledema, w/o hydrocephalus (n=3) papilledema w/ hydrocephalus (n=2)	hydrocephalus w/o papilledema (n=1)	Latency delay associated w/ hydrocephalus, but not papilledema	NR	In patient with hydrocephalus w/ papilledema VEP normalized s/p VP shunt, prior to papilledema resolution.
Rizzo, 1984 ¹²	Pattern reversal (check pattern)	27	IIH with papillary stasis (n=7), 2 w/ constricted VF	Controls (n=20)	Latency delayed in 2/7 IIH patients	Latency delayed exclusively in patients with VF constriction (n=2)	Latency shortened 24 hours after LP In patients with VF constriction (n=2)
Sørensen, 1985 ¹⁴ (overlap with Krogsaa)	Pattern reversal (check pattern)	33	IIH, all with papilledema, 3 w/ normal ICP (n=13)	Controls (n=20)	Latency delayed in IIH* 6/25 IIH eyes w/latency above control range	Latency associated with ICP* Latency not associated with papilledema degree or TVOs	Latency increase associated with progressive loss of vision (n=1) Latency decrease associated with resolution of papilledema (n=6)
Krogsaa, 1985 ¹³ (overlap with Sørensen)	Pattern reversal	35	IIH, all with papilledema (n=15), 12 with normal VF	Controls (n=20)	Latency delayed in IIH*	Latency delay preceded vision loss in patient who lost vision	Latency improved with papilledema resolution (n=8)
Bobak, 1988 ¹⁵	Pattern reversal (sinusoidal pattern, 2 temporal frequencies)	141	IIH (n=11), papilledema in 10, no visual field loss in 8, mild visual field loss in 3	Recovered optic neuritis (n=8) thyroid eye disease (n=7) controls (n=35)	4/11 IIH w/ abnormal transient latency or steady state phase no thyroid eye disease or optic neuritis with normal latency and phase	NR	NR
Verplanck, 1988 ¹⁶	Pattern reversal (check pattern, 3 spatial frequencies)	60	IIH (n=15)	Controls (n=45)	4/15 IIH w/ abnormal latency (5 eyes)	all eyes w/ abn VEP had abn CS 14/18 eyes w/ abn CS had nrl VEP 10/13 eyes w/ abn VF abn had nrl VEP	NR
Falsini, 1992 ²⁰	Pattern reversal (vertical sinusoidal)	39	IIH, grade 0–2 papilledema, minimal or no VF loss (n=18)	Controls (n=21)	Absolute amplitude and phase not different	9/10 IIH w/ VEP abnormality had PERG abnormality	NR

Recording/ study	stimulus	n	Papilledema subject details	comparison	findings	Correlation with other measures	Follow up
	pattern, multiple spatial frequencies)				between IHH and control subjects Normalized amplitude decreased at high frequencies in IHH and low frequencies in controls 10/18 IHH patients with at least one abnormality (phase or amplitude at any stimulus frequency)		
Mursch, 1998 ¹⁹	Flash VEP (n=48) Pattern reversal (n=4)	52	none	Craniostosis (n=52), 1 with optic atrophy, none with papilledema	Latency delayed in 12/52 Amplitude suppression in 2/52	NR	4/4 with pathological pre-operative VEP had improvement after ICP lowering surgery
Liasis, 2006 ¹⁸	Pattern reversal, ISCEV protocol	8	craniostosis w/ papilledema, high ICP (n=5)	Craniostosis w/o papilledema (n=3)	Latency normal in all Amplitude initially normal in all	NR	Amplitude decreased in all subjects prior to intervention and increased in all following ICP lowering surgery
Kesler, 2009 ¹⁷	Pattern reversal (check pattern)	20	Chronic IHH, 14 w/ abn fundus (swelling or atrophy), 6 w/ abn VF (n=20)	Lab norms	Latency prolonged in 11/20 w/ IHH	Latency prolonged in 12/14 eyes w/ abn fundus, 4/10 eyes w/ abn VF; 12/30 eyes w/ nrl VF	NR

n – number of subjects, LA – light adapted (photopic), DA – dark adapted (scotopic), ERG – electroretinogram, ICP – intracranial pressure, w/ - with, w/o – without, NR – not reported; VP – ventriculoperitoneal shunt, IHH – idiopathic intracranial hypertension, VF – visual field, LP = lumbar puncture, TVO – transient visual obscurations, abn – abnormal, nrl – normal, PERG – pattern ERG, ISCEV – International Society for Clinical Electrophysiology of Vision

Table 4

Studies reporting full field electroretinogram (FF-ERG), pattern electroretinogram (PERG) or pupillary light response (PLR) results in subjects with papilledema (in chronological order, * indicates statistically significant finding)

Recording/ study	stimulus	n	Papilledema subject details	comparison	findings	Correlation with other measures	Follow up
FF-ERG, PhNR							
Kirkham, 1981 ¹¹	Full field flicker (steady state)	2	brain tumor with papilledema (n=2)	Lab norms	ERG latency prolonged (L.A, DA)	VEP latency prolonged LA but not DA (see table 3)	Latency normalized with ICP improvement
Moss, 2015 ³¹	Full field red flash on blue background	25	IIH w/ optic nerve atrophy (n=2), mild papilledema (n=6), severe papilledema (n=2)	Controls (n=15)	PhNR prolonged in IIH* 6/10 IIH patients with abnormal PhNR	PhNR correlated w/ SAP mean deviation* PhNR correlated w/ ganglion cell atrophy and papilledema severity*	PhNR normalized w/ resolution of high grade papilledema in a patient w/ mild vision loss (n=1)
PERG							
Falsini, 1992 ²⁰	Pattern reversal (vertical sinusoidal pattern, multiple spatial frequencies)	39	IIH, grade 0- 2 papilledema, minimal or no VF loss (n=18)	Controls (n=21)	amplitude lower in IIH at intermediate/high spatial frequencies phase in IIH similar to controls Normalized amplitude decreased w/ increasing stimulus frequency in IIH and peaked at mid frequencies in controls 15/18 IIH w/ at least one abnormality (phase or amplitude at any stimulus frequency)	9/15 patients w/ abn PERG had abn VEP	NR
Afonso, 2015 ³⁵	Pattern reversal (check pattern, 2 spatial frequencies, ISCEV standard)	50	IIH (n=21) or VST (n=3), All resolved papilledema, stable, abn VF for 6 mo	Controls (n=26)	P50, N95, P50+N95 amplitude smaller in IIH for large checks* N95 latency longer in IIH for large checks* N95, P50+N95 amplitudes smaller in IIH for small checks* Latencies not affected for small checks AUC greatest for N95 large checks	Macular and peripapillary OCT thickness parameters correlated w/ N95 and P50+N95 amplitude for large checks* Macular OCT thickness parameters correlated w/ N95 and P50+N95 amplitudes for small checks* Visual field loss correlated w/ N95 and P50+N95 amplitudes for both stimulus sizes*	NR
PLR							
Park, 2016 ³⁹	Full field flashes (dim blue, bright blue, moderate red)	26	IIH, variable papilledema grade (n=13)	Controls (n=13)	Receiver operating characteristic for IIH vs. controls: 0.71 rod response (dim blue), 0.77 cone response (mod red), 0.83 melanopsin response	Sustained PLR amplitude (melanopsin response) correlated w/ SAP and log PhNR amplitude*	NR

Recording/ study	stimulus	n	Papilledema subject details	comparison	findings	Correlation with other measures	Follow up
					(bright blue), 0.90 combined response Response abn in 6/13 IHH (rod), 9/13 (cone), 6/13 (melanopsin)*		

PhNR – photopic negative response, n – number of subjects, LA – light adapted (photopic), DA – dark adapted (scotopic), VEP – visual evoked potential, ICP – intracranial pressure, IHH – idiopathic intracranial hypertension, w/- with, SAP – standard automated perimetry, VF – visual field, NR – not reported, ISCEV – International Society for Clinical Electrophysiology of Vision, VST – cerebral venous sinus thrombosis, AUC – area under curve, OCT – optical coherence tomography, abn – abnormal