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Clinical use of multifocal visual-evoked potentials in a glaucoma practice: a prospective study

Carlos Gustavo De Moraes,

Department of Ophthalmology, Einhorn Clinical Research Center, New York Eye and Ear Infirmary, 310 East 14th Street, New York, NY 10003, USA, New York University School of Medicine, New York, NY, USA

Jeffrey M. Liebmann,

Department of Ophthalmology, Einhorn Clinical Research Center, New York Eye and Ear Infirmary, 310 East 14th Street, New York, NY 10003, USA, New York University School of Medicine, New York, NY, USA

Robert Ritch, and

Department of Ophthalmology, The New York Medical College, Valhalla, NY, USA

Donald C. Hood

Departments of Psychology and Ophthalmology, Columbia University, New York, NY, USA

Carlos Gustavo De Moraes: demoraesmd@gmail.com

Abstract

Purpose—To test a framework that describes how the multifocal visual-evoked potential (mfVEP) technique is used in a particular glaucoma practice.

Methods—In this prospective, descriptive study, glaucoma suspects, ocular hypertensives and glaucoma patients were referred for mfVEP testing by a single glaucoma specialist over a 2-year period. All patients underwent standard automated perimetry (SAP) and mfVEP testing within 3 months. Two hundred and ten patients (420 eyes) were referred for mfVEP testing for the following reasons: (1) normal SAP tests suspected of early functional loss (ocular hypertensives, $n = 43$; and glaucoma suspects on the basis of suspicious optic disks, $n = 52$); (2) normal-tension glaucoma patients with suspected central SAP defects ($n = 33$); and (3) SAP abnormalities needing confirmation ($n = 82$).

Results—All the glaucoma suspects with normal SAP and mfVEP results remained untreated. Of those with abnormal mfVEP results, 68 % (15/22) were treated because the abnormal regions on the mfVEP were consistent with the abnormal regions seen during clinical examination of the optic disk. The mfVEP was abnormal in 86 % (69/80) of eyes with glaucomatous optic neuropathy and SAP damage, even though it did not result in an altered treatment regimen. In NTG patients, the mfVEP showed central defects in 44 % (12 of 27) of the eyes with apparently normal central fields and confirmed central scotomata in 92 % (36 of 39), leading to more rigorous surveillance of these patients.

Conclusions—In a clinical practice, the mfVEP was used when clinical examination and subjective visual fields provided insufficient or conflicting information. This information influenced clinical management.

Keywords

mfVEP; Glaucoma; Perimetry; Electrophysiology

Introduction

A diagnosis of glaucoma is based on the optic nerve appearance and visual fields, typically assessed by standard automated perimetry (SAP). Diagnostic ambiguity can arise when signs of glaucomatous optic neuropathy (GON) are present in the absence of visual field defects, or when such defects cannot be explained by the appearance of the optic disk or retinal nerve fiber layer (RNFL). The likelihood of glaucomatous damage being present increases when the location of structural loss corresponds to that of functional damage evidenced on SAP [1]. Other, newer technologies may help when there is disagreement between fundus evaluation and visual fields [2–7].

One such technology is the multifocal visual-evoked potential (mfVEP), an objective method for topographical assessment of visual function [8]. A number of studies have described how it has been used to identify glaucomatous damage [9–18]. We aimed not to describe the sensitivity/specificity of this technology to that of other tests; this has been done by other investigators. For instance, Fortune et al. [17] showed that the mfVEP and SAP tests have similar sensitivity/specificity. However, the results of mfVEP and SAP testing may disagree in 20 % of cases, suggesting that these modalities might detect different types of underlying diseases or somewhat different parameters involved in the physiologic visual pathway [16]. In any case, our purpose here is to understand how the mfVEP is used in the clinical practice of one of the authors (R.R.).

Based on our experience of over 8 years using this technique as a diagnostic tool, Hood and Ritch [19] suggested that the test was used for investigating cases with inconclusive SAP and disk exams, unreliable or inconsistent field tests, and SAP defects requiring confirmation. Figure 1a is a theoretical model that summarizes a decision process based on the current knowledge in the literature and illustrates outcomes that could potentially influence clinical decisions such as the initiation or advancement of therapy. However, clinical diagnosis is often challenging, and theory does not always match practice. To test whether this theoretical framework indeed describes the clinical process, we prospectively examined the use of the mfVEP technique during a 2-year period in a real-world clinical setting.

Methods

This was a non-randomized, prospective, descriptive study approved by the New York Eye and Ear Infirmary and Columbia University Institutional Review Boards. Written informed consent was obtained from all subjects and the study followed the tenets of the Declaration of Helsinki. The patients were referred for mfVEP testing between August 1, 2007, and July 31, 2009, by a single glaucoma specialist (R.R.).

Prior to mfVEP testing, patients underwent complete ophthalmic evaluation optic disk stereophotography and SAP testing (24-2 SITA-Standard, Humphrey Field Analyzer II, Carl Zeiss Meditec, Inc., Dublin, CA). Only eyes with gonioscopically open angles and signs of GON or ocular hypertension (any IOP ≥ 22 mmHg in at least one eye) were referred for mfVEP testing. GON was defined as a vertical cup-to-disk ratio >0.6 , asymmetry of the cup-to-disk ratio >0.2 between eyes, and/or the presence of localized RNFL or neuroretinal rim defect that could not be attributed to any other optic nerve or retinal cause. Because one

of our hypotheses was that the mfVEP may be useful in cases of unreliable or inconsistent SAP tests, all eyes with GON were enrolled regardless of the results and reliability indices of previous SAP tests. A reliable SAP result was defined as presenting fixation losses <20 %, and false-positive responses or false-negative responses <30 %. If any of the reliability indices did not meet these criteria, the test was considered unreliable. All eyes had visual acuities 20/40 and refractive errors <6.0D sphere or 2.0D cylinder.

Prior to referral, the physician was asked to state the reason for requesting the mfVEP test. Based upon prior experience [19], four main categories were created. In particular, all referred patients were placed into one of the following categories: (1) glaucoma suspects: GON and reliable SAP results within normal limits as defined by pattern standard deviation and mean deviation within the 95 % confidence interval and a GHT within normal limits on two consecutive tests; (2) ocular hypertension: no evidence of GON and IOP > 22 mmHg in both eyes during previous office visits and healthy optic disk/RNFL appearance with reliable SAP results within normal limits as defined in the previous group; (3) normal tension glaucoma: GON and reliable hemifield defects (further described) and at least five IOP measurements <20 mmHg without anti-glaucoma medications; (4) confirmation of SAP damage: typical GON and SAP defects as defined above. Since this group involved eyes with reliable and unreliable visual field tests, we further divided the group into 4a, to confirm the results of reliable tests, and 4b, to verify the results of unreliable tests. All patients had SAP tests performed within 3 months of the mfVEP.

The multifocal visual-evoked potential

The mfVEP was performed using VERIS 4.3 software (Electro-Diagnostic Imaging, San Mateo, CA), details of which have been described elsewhere [15]. In a single session, two 7-min recordings were obtained for monocular stimulation of each eye (right-eye followed by the left-eye). The estimated average setup time was approximately 10 min. Examples of mfVEP responses, together with probability plots obtained from a patient with open-angle glaucoma, are shown in Fig. 2. The points in these plots are positioned in the center of each of the 60 sectors of the display. A colored square indicates that the response was significant at either the 5 % (>1.96 SD, desaturated color) or 1 % (>2.58 SD, saturated color) level compared to normal values [12, 13, 15]. On the interocular plot, the color indicates whether it was the response of the left (red) or the right (blue) eye that was significantly smaller than the fellow eye. Measurements of mfVEP amplitudes were derived from signal-to-noise ratios (SNRs), which were calculated based on a method that has been described previously [15]. On the monocular plot, the color indicates that the SNR values of the left (red) or right (blue) eye for that location were significantly smaller.

Definition of abnormal hemifields

The assessment of the agreement between tests was based on hemifield damage. For the SAP and mfVEP tests, cluster criteria were used as previously defined [14–16]. In particular, for the SAP (PD plot), a hemifield was defined as abnormal if a cluster had two or more 8-way contiguous points at $p < 0.01$, or three or more contiguous points at $p < 0.05$ with at least one point at $p < 0.01$. To avoid rim artifacts, the cluster could contain no more than one point from the outer ring of the 24-2 SAP points. A central scotoma was defined if any of the cluster points, as defined above, fell within the 16 central points of the printout. The mfVEP from a hemifield was considered abnormal if it contained a cluster on the monocular or interocular plot of two or more contiguous points at $p < 0.01$, or three or more contiguous points at $p < 0.05$ with at least one point at $p < 0.01$.

Results

Two hundred and ten patients (127 women and 83 men) tested during the 2-year period met the inclusion criteria. Their mean age $\pm$ SD was 58.4 ± 13.2 years (range, 20–89). Most patients were of European (85 %) and Asian ancestry (11 %). The analysis of each group is shown separately below.

Glaucoma suspects

Fifty-two patients (104 eyes) were glaucoma suspects. All 104 eyes had normal SAP hemifields according to our criteria, while the mfVEP was abnormal in 22 (21 %). Figure 3 shows the SAP and mfVEP test of a patient from this group. The mfVEP showed an abnormal cluster of points in a region corresponding to a visual field location that had 2 abnormal points, but did not meet our criteria of abnormality.

Of the 82 eyes with a normal mfVEP, all remained untreated. Of the 22 eyes initially classified as glaucoma suspects and which had an abnormal mfVEP hemifield, 15 (68 %) were started on medication. The decision to treat these eyes depended on the presence of a corresponding rim/RNFL defect on the stereophotographs. The remaining 7 (32 %) eyes with an abnormal mfVEP were followed as glaucoma suspects and were not treated, although the level of surveillance increased with closer follow-up visits than those with no mfVEP abnormality.

Ocular hypertension

Forty-three patients (86 eyes) had ocular hypertension. The mfVEP was abnormal in 22 (25 %) of the eyes. Seven (32 %) of these remained untreated, while the other 15 started topical medication. There was no change of treatment in eyes with normal mfVEP results, whereas the 7 patients with abnormal mfVEP results remained untreated because other well-known risk factors (ocular hypertension treatment study: IOP, central corneal thickness, age, PSD, cup-disc ratio) put these patients in a low-risk group, which allowed them to be followed closely without immediate need of therapy.

Normal-tension glaucoma

Thirty-three patients (66 eyes) had mfVEP testing either to detect or to confirm central scotomata shown on the SAP printout. Figure 4 shows the SAP and mfVEP results of a patient with NTG who presented with a central defect OS and a suspicious paracentral region OD. The mfVEP interocular plot (Fig. 4b) confirmed both abnormalities.

Among the 39 eyes with central SAP defects, the mfVEP confirmed defects in 36 (92 %). Among the remaining 27 eyes without central scotoma on SAP, the mfVEP was abnormal in 12 (44 %). All eyes with central defects shown on the mfVEP were further tested with 10-2 strategy. Among those in which the mfVEP was consistent with the 24-2 defect, 33 (91 %) had an abnormal 10-2 result. Among those with a normal 24-2 but abnormal mfVEP, the 10-2 test was abnormal in 10 (83 %). All NTG patients were under medical or surgical therapy; no change in treatment occurred in this group of patients, except for closer follow-up visits.

Confirmation group

Eighty-two patients (164 eyes) were referred for testing to confirm an SAP abnormality. Of these, 44 (27 %) eyes had unreliable tests and 120 (73 %) had reliable indices.

Unreliable SAP tests (4a): In 22 (50 %) eyes, the mfVEP showed no hemifield abnormalities. This finding did not result in any change on treatment. In the other 22 eyes in

which the mfVEP showed at least one abnormal hemifield, the result of the mfVEP was further used to define the extent of functional loss. All eyes were already on medication, and there was no change in treatment after testing.

Reliable SAP tests (4b): The SAP result was abnormal in 114 (47 %) hemifields and 80 (56 %) eyes. The mfVEP confirmed SAP defects in 87 % (99/114) of the hemifields and in 86 % of the eyes (69/80). The mfVEP result did not change the management of any patient in this group, as they were already all being treated medically. However, it allowed us to confirm the extent of damage of eyes in which the optic nerve/RNFL appearance did not match the results of the visual field.

Figure 5 depicts a patient in whom the mfVEP was consistent with the abnormal SAP test. The optic nerve showed significant thinning of both the superior and inferior rim. However, the functional defect was confined to the inferior hemifield both on the SAP and on the mfVEP results (Fig. 5c, d).

Based upon these results, we modified our initial framework in order to better describe how the mfVEP technique was used in this clinical practice (Fig. 1b). Table 1 compares medical interventions based on mfVEP results. All eyes with normal results remained untreated, whereas over half of those with abnormalities were either started on or remained on topical treatment.

Discussion

We prospectively examined how the mfVEP technique was used in a glaucoma referral practice to aid in the management of patients. In particular, patients with inconclusive SAP and disk exams, unreliable or inconsistent field tests, or SAP defects requiring confirmation were tested with the mfVEP.

In glaucoma suspects (presence of GON with normal SAP), the mfVEP was normal in 79 % of eyes. None of these patients were treated. Therefore, a normal mfVEP outcome in a glaucoma suspect was interpreted by the clinician as suggestive of low risk of glaucoma. Obviously, this decision was not solely based on the test result, as the normal mfVEP could be a false-negative. Rather, normal results of two functional tests (one objective and the other subjective) coupled with the findings during clinical examination significantly lowered the level of suspicion for those patients. Conversely, 21 % of the suspect eyes had abnormal mfVEPs, which was interpreted as a potential sign of early glaucoma damage, and those with abnormalities consistent with clinical examination were treated.

In a clinical practice where patients range from normal to borderline to glaucoma, narrowing the group of borderline cases (glaucoma suspects) serves to initiate early treatment for those at increased risk of progressive glaucoma and decreases the number of patients treated unnecessarily. Our initial hypothesis of how the mfVEP technique was used in cases of patients with suspected glaucoma or ocular hypertension came from our clinical impressions, as well as from studies such as Graham et al. [21], who found that 18 % of high-risk glaucoma suspects showed mfVEP defects, and Thienprasiddhi et al., [18] who found that the mfVEP was abnormal in 20 % of glaucoma suspects and 14 % of ocular hypertensives. Also, mfVEP deficits were shown in hemifields with supposedly normal SAP results when the opposite hemifields had SAP defects [22], indicating a potential use of the mfVEP technique for detecting early glaucomatous damage before it can be detected by SAP. We observed similar findings in our ocular hypertensive patients and glaucoma suspects, in whom the mfVEP was abnormal in 25 and 21 % of eyes, respectively. Even though false-positive results are inherent of any diagnostic technique, previous reports using the mfVEP technique have shown a range between 0 and 3 % [10], as well as fairly good

sensitivity and specificity compared with other technologies [20]. In any case, the decision of treatment in suspect eyes with an abnormal mfVEP depended on the presence of a corresponding rim/RNFL defect during clinical evaluation.

In patients tested to confirm a visual field defect, we found that in glaucomatous eyes with established, reliable SAP abnormalities, the mfVEP confirmed 87 % of the affected hemifields (86 % of eyes). Fortune et al. [17] found that the mfVEP and SAP agreed in 75–81 % of early glaucomatous eyes. Even though the mfVEP results did not lead to any change in treatment, it was used by the clinician to better determine the extent of functional damage and increase the level of surveillance over areas that showed normal SAP but abnormal mfVEP.

As expected, we found that the mfVEP can be helpful in cases of unreliable SAP tests [19]. The objective nature of the technique offers an advantage over VFTs of visual function. In our study, a normal mfVEP result in cases of unreliable SAP tests had a strong effect on clinical decision. In particular, these patients were not treated. Conversely, an abnormal result was taken as a true defect when corroborated by optic nerve findings. It is important to emphasize that we are describing how the mfVEP technique was used; we are not suggesting that it is a gold standard. Again, one should take into consideration the inherent false-positive rates of the mfVEP technique in the confirmation group as well. We tried to minimize this effect by comparing the mfVEP results with the 24-2 tests and optic disk appearance.

Finally, in eyes with NTG, the mfVEP confirmed 92 % of the central scotomata seen on SAP. Moreover, the mfVEP showed central abnormalities in 44 % of the eyes with apparently preserved central function on SAP. On one hand, some of these abnormalities could be false-positive results due to poor fixation or low signal-to-noise during mfVEP testing. On the other hand, eyes with NTG tend to present with central defects more often than eyes with high tension glaucoma [23, 24], so it is possible that the mfVEP showed better sensitivity in detecting a central abnormality. This could be explained by the fact that the mfVEP technique has a more dense representation of the central field than the 24-2 SAP [15]. The presence of deficits close to fixation threatens the patient's visual acuity and might change the classification of their level of damage to severe which often demands more aggressive therapy. The mfVEP can be used to detect central defects not shown in the 24-2 strategy, although the relative efficacy of the mfVEP and 10-2 in detecting central defects remains to be determined. Although no change in treatment regimen of patients with NTG was observed in our study, the level of surveillance increased during further follow-up.

A previous study also investigated the applicability of the mfVEP technique in a clinical scenario [23]. This retrospective study showed the usefulness of the technique in a large sample (436 subjects over a 1-year period). As in our study, the mfVEP test was found to be valuable in categorizing subjects with unreliable, unconfirmed or excessively subjective field defects. In addition to being prospective, our study adds to these findings in showing the usefulness of the mfVEP in NTG and documenting how mfVEP results changed treatment based on the correlation between the location of the abnormalities seen with mfVEP and the defects observed during clinical examination of the optic nerve and RNFL. It should be noted, however, that it was not our purpose to compare the diagnostic ability of the mfVEP to that of other technologies, nor can we rule out that the possibility that the diagnostic power of detecting glaucoma could be increased by replacing the mfVEP test with other diagnostic tests (e.g., SWAP) or even repeated conventional perimetry. Instead, we sought to describe how the mfVEP was used in a clinical practice, as despite extensive debate on the performance of each technique, little is known on how they are used in practice and how they influence clinical decisions.

This prospective, descriptive study confirmed our initial impression [19] about how the mfVEP technique was used by a glaucoma specialist in situations when he needed to confirm SAP defects and when the tests were inconclusive or inconsistent with clinical findings. Figure 1b shows the revised decision flow chart based on our new findings. In addition, we found that the mfVEP influenced management when tests were inconclusive and the specialist needed to rule out early damage, as in the case of suspects and ocular hypertensives.

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Fig. 1.

a Flow chart based on our initial impression of how the mfVEP technique could be used in cases of normal or unreliable standard automated perimetry (SAP) tests. In order to be included, patients either had to have glaucomatous optic neuropathy (GON) or intraocular pressure (IOP)>22 mmHg.

b A modified flow chart after testing our initial framework in **a**. *GON* glaucomatous optic neuropathy, *IOP* intraocular pressure, *SAP* standard automated perimetry, *GS* glaucoma suspect, *OHT* ocular hypertension, *NTG* normal-tension glaucoma, *mfVEP* multifocal visual-evoked potential technique

Fig. 2.

Examples of mfVEP probability plots of a patient with glaucoma. The diameter of the display subtended 44.5°. The sectors, and the checks, are scaled to be of approximately equal effectiveness, based upon cortical magnification factors. For example, the inner-most sectors are about 1.2° in width while the outer-most sectors exceed 7° in width. **a** Interocular probability plot. **b** monocular probability plots. A *colored square* indicates that the mfVEP response was significantly smaller in the right (*blue*) or left (*red*) eye at either the 5 % (desaturated color) or 1 % level (saturated color)

Fig. 3.
a Standard automated perimetry (SAP) and **B** mfVEP results from a suspect glaucoma eye. The disk photograph **c** revealed inferior neuroretinal rim loss (*arrow*). Despite presenting a SAP test within normal limits, the mfVEP showed a superior defect that could be interpreted as an early damage (*red dashed oval*)

Fig. 4. Example of mfVEP of a normal-tension glaucoma patient. Note that the central scotoma (**a**, red dashed squares) was confirmed by the mfVEP in both eyes (**b**, red dashed oval)

Fig. 5. Example of patient in whom the mfVEP (*red arrows*) was used to confirm an abnormal standard automated perimetry (SAP) test (*pink rectangle*). Optic disk photography showing significant thinning of both the superior and inferior rim (**a**, *black arrows*)

Table 1

Management of eyes with normal SAP fields (ocular hypertensives + glaucoma suspects) in terms of the results of their mfVEP ($n = 190$ eyes)

mfVEP results management	Normal	Abnormal	Total
Treatment	0	30	30
No-treatment	146	14	160
Total	146	44	190