Tracking the Recovery of Local Optic Nerve Function after Optic Neuritis: A Multifocal VEP Study

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PURPOSE. To explore the multifocal visual evoked potential (mVEP) as a technique for tracking local optic nerve damage after unilateral optic neuritis (ON).

METHODS. Humphrey visual fields and mVEP recordings were obtained from three patients within 7 days of an episode of ON. Patients were retested during the recovery phase, approximately 4 to 7 weeks later. The multi-input procedure of Sutter was used to obtain 60 local VEP responses (the mVEP) to a scaled checkerboard pattern. The mVEPs were recorded separately for monocular stimulation of both eyes.

RESULTS. Initially, all three patients had extensive visual field defects, reduced visual acuity, and depressed mVEP amplitude in regions of poor visual field sensitivity. By 4 to 7 weeks, the fields recovered to near normal sensitivity in most locations, and visual acuity returned to 20/20. The mVEP recovered to nearly full amplitude in all regions, but substantial delays were present in many locations. The delayed responses were associated with regions of visual field loss documented during the acute phase.

CONCLUSIONS. The mVEP can be used to track local optic nerve damage after unilateral ON. This technique should be useful in observing the effects of treatments as well as in testing hypotheses about the mechanisms underlying both the acute loss of vision and the subsequent recovery. (Invest Ophthalmol Vis Sci. 2000;41:4032–4038)

Optic neuritis (ON) is a clinical syndrome characterized by an acute, unilateral loss of visual function accompanied by an afferent pupillary defect. If examined acutely, approximately 40% of the patients have a swollen optic nerve head, and virtually all patients exhibit visual field defects characteristic of optic nerve disease. ON typically occurs in adults younger than 45 years and is more frequently seen in women. After the acute episode, visual function usually recovers within 3 months. Unless other causes can be identified (e.g., syphilis, sarcoid, cat scratch disease, or autoimmune causes), ON is thought to be a manifestation of multiple sclerosis. With the advent of experimental drugs designed to impede the course of multiple sclerosis, it is increasingly important to follow changes in visual function. Visual field tests, such as Humphrey perimetry, may not be up to this task. In many cases, visual fields appear normal after recovery, although visual symptoms persist. However, these patients often exhibit abnormal visually evoked potentials (VEPs). Almost 30 years ago, Halliday et al. reported delayed VEP responses after episodes of ON and noted that these delays could be present after recovery, even when field abnormalities could no longer be detected. Subsequent work confirmed and extended these findings (see References 4 and 5 for reviews). In a recent study, 77% of 90 patients experiencing ON exhibited abnormal VEPs during the acute phase. The VEP returned to normal in 19% of those patients with initially abnormal VEPs and became abnormal in approximately half of those with initially normal VEPs. It is not clear, however, to what extent these different patterns are due to true differences in the acute and recovery phases of these patients, rather than differences in the regions dominating the VEP response. The traditional VEP is a mix of responses from unaffected and affected regions and will be dominated by regions of the optic nerve producing the largest responses. Thus, we do not know whether there are abnormal regions of the optic nerve in those patients with normal VEP responses or normal regions of the optic nerve in those patients with abnormal responses. In the current study, we explored the multifocal VEP as a possible means of observing early local changes.

With traditional VEP techniques, responses can be obtained at only a few field locations within a single testing session. However, by using the multiple-input method of Sutter, Baseler et al. showed that 60 or more local VEP responses, called the multifocal VEP (mVEP), could be obtained over a wide region of the field if the stimulus array was scaled to roughly account for cortical magnification (Fig. 1A). With this technique, local field defects can be detected in patients with ganglion cell and/or optic nerve damage, as shown by Klistorner et al. For the study of unilateral damage, this technique can be improved by comparing the mVEP responses obtained from monocular stimulation of each eye. The monocularly driven mVEP responses are essentially identical in nor-
METHODS

Subjects

Table 1 provides basic information about the three patients in this study (denoted Patients 1, 2, and 3). All three had right-side afferent pupillary defects on first examination. Magnetic resonance imaging (MRI) scans were obtained within a week of the onset of ON. All three patients showed enhancement of the optic nerve. Two patients (2 and 3) also showed multiple hyperintensities on the FLAIR images of the MRI. The diagnosis of multiple sclerosis was made based on ON and the MRI in the case of Patient 3 and in the case of the other (Patient 2) based on ON, the MRI and previous neurologic symptoms as well as asymmetric, long track findings on medical examination. In the case of Patient 1, the rest of the neurologic examination and MRI were negative, but she exhibited Uhthoff symptom. Informed consent was obtained from all subjects before their participation. Procedures followed the tenets of the Declaration of Helsinki, and the protocol was approved by the committee of the Institutional Board of Research of Columbia University.

The mVEP Stimulus

The stimulus array was produced with visual evoked response imaging system (VERIS) software (Dart Board 60 With Pattern; Electro-Diagnostic Imaging [EDI], San Mateo, CA). The stimulus (Fig. 1A) consisted of 60 sectors, each with 16 checks, 8 white (200 candelas [cd]/m²) and 8 black (<3 cd/m²). The entire display had a radius of 22.2°. The sectors were scaled; the central 12 sectors fell within 2.6° of the foveal center (Fig. 1A, insert). The stimulus array was displayed on a black and white monitor driven at a frame rate of 75 Hz. The 16-element checkerboard of each sector had a probability of 0.5 of reverting on any pair of frame changes and the pattern of reversals for each sector followed a pseudorandom (m) sequence. For a more detailed description of the general multifocal technique see Reference 6 and for more information about the mVEP see References 7 to 9.

Visual Fields

Humphrey 24-2 or 30-2 visual fields were obtained using the SITA-FAST program (Humphrey, San Leandro, CA). The spatial relationship between the test spot locations of the 24-2 visual field and the sectors of the multifocal stimulus is shown in Figure 1B. The total deviation values for the fields obtained during each patient’s first visit are shown in Figure 2 as probability plots. To allow a comparison of the visual field sensitivity to the mVEP responses, an estimate of sensitivity for each sector of the multifocal stimulus was obtained from the visual field values. These estimates were obtained by computer (Matlab software; The Mathworks, Natick, MA) and the following interpolation procedure. First, the antilog of the Humphrey deviation value (the numbers underlying the points in Fig. 2) was calculated. For each sector of the multifocal stimulus, the location on the visual field and the sectors of the multifocal stimulus is shown in Figure 1B. The total deviation values for the fields obtained during each patient’s first visit are shown in Figure 2 as probability plots. To allow a comparison of the visual field sensitivity to the mVEP responses, an estimate of sensitivity for each sector of the multifocal stimulus was obtained from the visual field values. These estimates were obtained by computer (Matlab software; The Mathworks, Natick, MA) and the following interpolation procedure. First, the antilog of the Humphrey deviation value (the numbers underlying the points in Fig. 2) were calculated. For each sector of the multifocal stimulus, the location on the visual field and the corresponding sensitivity estimate were obtained. These estimates were then averaged over all sectors of the multifocal stimulus to obtain a single overall sensitivity estimate for each patient. To allow a comparison of the visual field sensitivity to the mVEP responses, an estimate of sensitivity for each sector of the multifocal stimulus was obtained from the visual field values. These estimates were obtained by computer (Matlab software; The Mathworks, Natick, MA) and the following interpolation procedure. First, the antilog of the Humphrey deviation value (the numbers underlying the points in Fig. 2) were calculated. For each sector of the multifocal stimulus, the location on the visual field and the corresponding sensitivity estimate were obtained. These estimates were then averaged over all sectors of the multifocal stimulus to obtain a single overall sensitivity estimate for each patient.
was obtained for each test location in the visual field. Using a linear algorithm, these values were interpolated into a high-resolution surface. To obtain the interpolated value for a given sector of the mVEP display, the interpolated values within the region covered by that sector were averaged, and the log of this average value was determined. This procedure was repeated for each eye. The interpolated fields in Figure 3 were obtained by subtracting the values (in decibels) of the left eye from those of the right. These differences between the monocular values are displayed in sectors with equal diameters for clarity of presentation; the relationship to linear coordinates can be determined by relating the bold circles in Figure 3A to the colored circles in Figure 1. Note that the antilogs of the Humphrey deviation values were averaged rather than the decibels (i.e., log) values. Commonly, the decibel values of visual fields are averaged. Although, in most (but not all) cases, it does not make much difference whether the log or antilog values are averaged, the assumptions behind our approach in this study are easier to defend, especially in the case of damage to the optic nerve (Note: The logic is best illustrated with an example. Suppose that half of a patch of retina covered by an mVEP sector is normal and the other side is missing all the ganglion cells or related optic nerve fibers. The Humphrey deviation values for these two sides should be 0 [normal sensitivity] and approximately −30 [the maximum loss measurable at that point]. The average of the antilog of these values is approximately 0.5 [−3 dB]—that is, one half of normal. The average of the dB values is −1.5 or one thirty-second of normal. The comparison of visual fields to electrophysiological measures requires assumptions. We are more comfortable with the assumption that one half the optic nerve fibers will yield one half the normal mVEP amplitude as opposed to only one thirty-second of the normal mVEP amplitude.)

RESULTS

Acute Phase

Figure 2 contains the Humphrey Total Deviation probability plots obtained shortly after the onset of ON. All three patients showed regions of depressed sensitivity in the visual fields. Figure 1C contains the mVEP records from Patient 1. The responses from the right eye (blue records) were smaller than those from the left eye (red records) over large portions of the field. To aid in comparing the visual fields with the mVEP responses, the contours, shown in color in Figure 1 and in bold for Figure 3A, were added to this figure. These were isodensity contours for circles with diameters of 22.2°, 9.8°, and 2.6°. It is now easier to see that the responses in the right eye were smaller in regions in which the field sensitivity was depressed. However, it is still not easy to compare the patient’s mVEP records (Fig. 1C) to her visual fields (Fig. 2A) because of the difference in spatial representation. The positions of the individual mVEP records did not correspond to the locations of the sectors in Figure 1A. If they had, the central records would overlap. Further, individual test locations of the Humphrey field did not fall in the same place in each sector (Fig. 1B). The interpolated visual field display was developed to deal with these problems.

Figure 3A (left) shows an interpolated visual field for Patient 1. Each sector in the figure corresponds to one of the sectors of the mVEP display, but these sectors are shown with equal diameters for ease of presentation. The Methods section describes the procedure used, and the circles in Figure 1D and Figure 3A illustrate the spatial relationship of the interpolated field to the mVEP display. The number in each sector of a field describes the procedure used, and the circles in Figure 1D and Figure 3A illustrate the spatial relationship of the interpolated field to the mVEP display. The number in each sector of a field indicates the number of responses in regions of similar sensitivity. Averaging has the dual advantage of increasing the signal-to-noise ratio of the records and allowing a picture of the results that is easier to interpret than the full 60-response array in Figure 1C. Figure 4 shows mVEP responses from a control subject. The mVEP responses were averaged within groups of six sectors, as shown in the figure. As previously described,7–12 the waveforms differed markedly with retinal location. These groups were chosen because the waveforms within each group tend to be similar for control subjects9,12 and because, in the cur-
rent patients, these groupings allow a comparison between regions of reasonably good and relatively poor sensitivity.

Figure 5 shows the mVEP responses for the three patients averaged for the same groups of six sectors. Each record is the average for the two 7-minute recordings. Figure 4B shows the group responses for the individual recordings behind the averaged records in Figure 5A. The repeat reliability is quite good.

There are three conclusions to be drawn from Figure 5. First, when the affected eye’s sensitivity is depressed relative to the unaffected eye, then the mVEP responses from the affected eye are substantially smaller (see response pairs labeled 1). Second, substantially depressed responses can be seen in regions where there were relatively small differences (i.e., 3 or 4 dB) in sensitivity between the eyes (see response pairs labeled 2). Third, the responses can be reasonably large in regions where the affected eye’s sensitivity is nearly the same (within 2 dB) as the unaffected eye’s sensitivity (see response pairs labeled 3). (In some regions, the responses from the good eye were too small for a useful comparison to be made. These response pairs were not labeled with a number in Figure 5. This does not imply that the good eye was abnormal, because similar small responses can be seen in control subjects [see Fig. 4 and References 7 to 9].)

**Recovery Phase**

Figure 3 (right columns) contains the interpolated fields for various times after the onset of ON. The mVEPs were obtained on the same visit, except in the case of Patient 1 (at 2.5 weeks) for whom we were unable to schedule an mVEP recording. Note that the fields had largely recovered within 7 weeks for Patients 1 and 3 and within 4 weeks for Patient 2. For Patients 1 and 2, the affected eye was within 3 dB of the unaffected eye at all locations and, in many locations, it was as sensitive as the unaffected eye. For Patient 3, the field for the affected eye was slightly, but not significantly better. The amplitude of the mVEP responses had also recovered. Figure 6 shows the mVEP responses obtained 4 to 7 weeks after the onset of ON and summed, as in Figure 4, in groups of six sectors. There are two conclusions to be drawn from this figure. First, the mVEP responses from the affected eye had recovered and were typically very close in amplitude to those from the unaffected eye. Second, most, but not all, of these recovered responses were substantially delayed. The delays were not the same within a patient or across patients. All three patients had regions of marked delays and regions where the delays, if present, were relatively small. Further, Patient 3 who had the most profound field loss during the acute phase, showed the smallest delays 7 weeks later. (Note that when interpreting small differences in
The differences between the latency of the records from nasal and temporal retina must be considered [Fig. 4 and Reference 9]. In the records from control subjects, the responses from the left eye were slightly faster [approximately 4–5 msec] in the left visual field and slightly slower in the right visual field. It has been suggested that this small timing difference occurred because an action potential initiated in the nasal retina, compared with the temporal retina, had a shorter distance to travel to arrive at the optic disc.9,13)

The delayed responses in Figure 6 are associated with regions showing field losses during the acute phase. In the case of Patient 1, all the regions with delays in Figure 6 showed field defects at either 3 days or 2.5 weeks. Similarly, Patient 2 showed more profound delays in the lower field compared with the upper field (Fig. 6B) in agreement with the visual field obtained during the acute phase (Figs. 2B, 3B).

Permanent Defects

Although all three of the patients studied recovered field sensitivity, patients with ON are often left with local field defects. These regions of permanent sensitivity loss are probably associated with depressed mVEP amplitudes.9,14)

Reproducibility and Tracking Changes within an Eye

Figure 8 shows the mVEP records for Patient 2 from Figure 5B (black) along with responses recorded more than 3 months later (gray). The upper set of records for each region is from the unaffected (left) eye, and the lower set is from the affected (right) eye. As previously shown,7,12 the records for the unaf-
fected eye show good reproducibility, suggesting that it should be possible to track local changes over time using a within-eye comparison. That the responses from Patient 2’s affected eye are also very similar further suggests that the underlying disease in this patient was reasonably stable between 4 and 17 weeks. Consider also the records in Figure 8B from Patient 1. The records in gray were obtained at 3 days and are the records labeled 3 in Figure 4A. The corresponding records from Figure 6A obtained at 7 weeks are shown as the black records. The responses recorded at 7 weeks from the affected eye appeared to be delayed relative to those recorded at 5 days, presumably because of the effects of a demyelinating process during this period.

**DISCUSSION**

The evidence here suggests that the mVEP can be used to track local optic nerve damage after ON. First, the mVEP recordings showed good reproducibility over time in control subjects.7,12 In Figure 8, the records obtained 3 months apart for patient 2
are very similar. Second, the mVEPs obtained in the recovery period showed clear differences between the two eyes, even in regions where the field sensitivity was essentially identical. The mVEP was clearly superior to the visual field in identifying abnormal regions. Finally, according to the mVEP records, all regions of the affected eye were not equally affected. If they were, the mVEP would lose some of its advantage over the traditional VEP. Note in Figures 6A and 6B, for example, that pairs of mVEP responses from Patients 1 and 2 showed a range of timing differences from a few milliseconds (close to normal) to extreme delays. Further, for Patient 1 at 3 days (Fig. 4A), mVEP amplitudes ranged from near normal to nondetectable. Similarly, the mVEPs from the patient studied 21 years after acute ON showed local differences (Fig. 7). In sum, for assessing local optic nerve damage, the mVEP had clear advantages over both the behavioral visual field and the traditional VEP techniques.

Although the mVEP may offer clear advantages, how best to exploit these advantages remains open. Optimal stimulus conditions have yet to be explored. Further, the number of recording electrodes and their positioning is under study, as is the optimal way to analyze mVEP data. It is known, for example, that the unaffected eye can have an abnormal traditional VEP (35% of the cases in a recent study). In these cases, the interocular comparison described here may still be adequate to observe the relative changes in each eye. However, the amplitude and implicit time of local responses such as those in Figures 5 through 8 could be compared with control group values, much as has been done for the traditional VEP. Or, for observing changes over time in the same eye, Fig. 8 suggests serial mVEPs from the affected eye may be all that is required. In any case, the best way to exploit the advantages of this new technique to study ON remains to be determined.

Finally, although the mVEP technique is new, our observations about the effects of ON on the VEP are not. Numerous studies have confirmed and extended the early conclusions of Halliday et al. mentioned in the introduction. The most common finding is a markedly reduced and delayed VEP during the acute phase. During the recovery phase, the response is generally found to increase in amplitude but to remain delayed. However, VEPs with abnormal amplitude but normal timing, VEPs with abnormal timing and normal amplitude, and nondetectable VEPs have been reported in both the acute and recovery phases. We saw nearly all these possible outcomes in the four patients studied. It is of interest that each patient showed two or more patterns within a single field—information that is lost in the traditional VEP. Thus, although the basic observations in this study are not new, the ability to track local changes is. This should allow the study of local effects of both the disease process and drug therapies.

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References