Further Evidence for the Utility of Electrophysiological Methods for the Detection of Subclinical Stage Retinal and Optic Nerve Involvement in Diabetes

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Introduction

Diabetic retinal neuropathy and optic nerve involvement are frequent complications of diabetes, but they receive little attention in ophthalmological practice since diabetic retinopathy is discussed almost exclusively as vascular retinopathy (i.e. retinal involvement that is evident on fundoscopy) in textbooks and in the literature [1, 2]. Vascular retinopathy, however, is mostly a late complication [3], only rarely manifest at the time of diagnosis [4]. A patient diagnosed with diabetic retinopathy has approximately a 50% chance of losing vision in 5 years [3], which in itself calls for efforts to detect retinopathy at the earliest possible stage.

Several methods have been suggested for the detection of subclinical retinopathy, such as fluorophotometry [5] and various electrophysiological methods [3, 6–8]. Evidence suggests that the electrophysiological methods are sensitive and reliable indicators of the retinal and optic nerve involvement in diabetes. However, the literature on this topic is relatively limited, and the significance of electrophysiological methods is clearly underestimated.

In this study, the aim was to provide further evidence for the utility of two electrophysiological methods [vi-
In this retrospective study, data of 63 type I diabetes patients with no clinically manifest (vascular) retinopathy were analyzed. The patients were divided into two groups based on the presence or absence of polyneuropathy. Diabetic polyneuropathy was assessed with Neurotometer (Neurotron, Inc., Baltimore, Md., USA) and the Ewing test. The assessment was done by an experienced internist who routinely uses for stimulation. RCT = Retinocortical time.

For the VEP recordings, the recording electrode (gold cup) was taped on the Oz site, the reference electrode on the Cz site, and the ground electrode was placed in the Fz site (similarly to VEPs). For the evaluation of VEP alterations the N75, P100 and N135 latencies and the P100 and N135 amplitudes were used. For the evaluation of PERG alterations the N75–P100, μV and N135–P100, μV peak times and the P100 and N135 amplitudes and their ratios (N95/P50) were calculated.

For the PERG recordings, Black and white checkerboard patterns were used for stimulation. Filters were set between 1 and 100 rps for both VEPs and PERGs. The viewing distance was 1 m, and the stimulus display subtended a 12° by 16° area. The contrast was 97%. One hundred responses were averaged for VEPs and 200 responses for PERGs. To test trial-to-trial variability, all tests were repeated in the same session after a break of 2 min. Monocular stimulation was applied for VEPs and binocular stimulation for PERGs.

The results were compared with the reference datasets of our laboratory (tables 1, 2).

For the comparisons, the Mann-Whitney U test was used, as the criterion of normal distribution was not met. The level of significance was adjusted according to the Šidak correction: \( a_1 = 1 - (1 - \alpha)^1/n \) where \( a_1 \) is the adjusted p level and \( \alpha \) is the default p level.

### Subjects and Methods

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Data from both eyes of each patient were included in the analysis, so as to avoid bias and misinterpretation [11, 12]. The results were compared with the reference datasets of our laboratory (tables 1, 2).

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level (0.05), and n is the number of independent comparisons. The adjusted level of significance was $p = 0.01$. Statistical analyses were conducted in SPSS 21.0 (IBM, USA).

For stimulation and recording, a Roland Electrophysiological Test Unit was used, with the RETIport 32 software (Roland Consult, Brandenburg an der Havel, Germany). Before the tests, the refractive errors of the eyes were determined and corrected for viewing distance.

Statement of Ethics
The study was designed according to the Declaration of Helsinki, and it was approved by the Biomedical Research Ethics Committee of the University of Szeged. All patients were informed that their medical data would be used for research purposes, and written informed consent was requested from all the 63 patients. Data were used only upon consent.

Results

The mean age in the polyneuropathy group was 47.4 years (range: 20–74 years). The mean diabetes duration in this group was 15.2 years (range: 1–40 years). The mean age of the polyneuropathy-free group was 49.1 years (range: 21–74 years). The mean diabetes duration in this group was 14.9 years (range: 1–40 years).

In the polyneuropathy group, VEP was abnormal in 76 (100%) eyes, and this was accompanied by PERG alterations in half of the cases, while in the polyneuropathy-free group, VEP was abnormal in 40 eyes accompanied by abnormal PERG in 38 (95%) eyes. Normal electrophysiological responses were not found in the polyneuropathy group, while in the polyneuropathy-free group normal responses were recorded from 10 (20%) eyes. Examples of the characteristic alterations are shown in figure 1. In the polyneuropathy group, the leading alteration was an abnormal delay of P100 which was seen in 62 (82%) eyes. Doubled P100 peaks and abnormally broad waveforms were also observed but only sporadically (doubled peaks in 6 eyes and broad waveforms in 8 eyes).

PERG findings were abnormal in 38 (50%) eyes. Of the 76 eyes, P50 peak time was delayed in 28 (37%) eyes, and in 16 eyes subnormal P50 (N35–P50) and N95 (P50–N95)
peak-to-peak amplitudes were found (21%). The depression of the N95 amplitude was particularly characteristic (table 1).

In the polyneuropathy-free group, the most frequently observed alteration was also an abnormal P100 delay which was seen in 21 (42%) eyes. As for the most frequent PERG abnormalities in this group, P50 peak time was delayed in 24 (48%) eyes, and subnormal P50 and N95 amplitudes were found in 11 (22%) eyes (table 2).

Discussion

In this study, the VEP and PERG were sensitive indicators of subclinical retinal and optic nerve involvement in diabetes even at an early stage when the patients were free of neuropathy and the fundus showed no signs of retinal involvement. These methods are also less time-consuming than normal and multifocal ERGs that require dark adaptation and pupil dilation [13]. Equally important, PERG and VEP are best used in combination for the purposes of ophthalmological screening in diabetes. Given the continuity of the optic nerve with the retina, an abnormal VEP recording could indicate either optic neuropathy or retinopathy or both. This differential diagnostic problem would be resolved by the simultaneous use of electroretinography.

As for the specific abnormalities found in this study, especially the peak delays and subnormal responses appear to be characteristic of the studied diabetic patient populations, while less frequent alterations, like double P100 peaks, definitely require further corroboration. However, it must be taken into consideration that the aim of this study was not to categorize the alterations that can be found early in the course of disease progression, but to investigate if they can be found at all. Our results show that the alterations can be detected, and we suggest that the qualitative details be considered as data to be confirmed or disproven by later studies.

Conclusions

Our findings showed that PERG and VEP were sensitive tools for the early detection of neural damage, well before the retinal involvement becomes evident on fundoscopy. Therefore, we suggest that regular electrophysiological screening should receive more attention in the ophthalmological care of diabetic patients with the diagnosis of the disease.

Acknowledgments

Prof. György Benedek was supported by the OTKA Hungary Grant No. K83810. The authors would like to express their gratitude to Prof. Michele G. Shedlin at NYU College of Nursing for her assistance with editing.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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