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# Subclinical Optic Neuropathy in Graves' Orbitopathy

Gölge Acaroğlu*, Tülay Şimşek†, Solmaz Özalp‡ and Ayşe Mutluay§

*Departments of *Neuro-ophthalmology, †Glaucoma, ‡Electrophysiology and §Strabismus, Social Security Eye Hospital, Ankara, Turkey*

**Purpose:** The aims of the study were to detect early changes in the optic nerve function of patients with Graves' orbitopathy (GrO) who do not have any signs and symptoms of optic neuropathy, using pattern visual evoked potentials (P-VEP), and investigate any possible relation between the disease activity and P-VEP P100 latencies of the patient group.

**Methods:** The study was conducted in a tertiary care hospital. Sixteen patients with GrO and 15 healthy controls were enrolled. P-VEP P-100 latencies were compared between these two groups. Correlation between the clinical disease activity and P-VEP P-100 latencies of the patient group was also investigated.

**Results:** Mean P-VEP P-100 latency values were significantly different in the GrO ($122.0 \pm 14.40$ ms) and control groups ($105.9 \pm 7.7$ ms) ($P = .0004$). The GrO patients' P-100 latencies correlated mildly with their activity scores ($r = .364$, $P = .0406$).

**Conclusions:** Clinical application of the P-VEP for the assessment of visual function in patients with GrO proved useful for early diagnosis of the optic nerve involvement, and it may be more valuable in patients with "active" congestive disease. **Jpn J Ophthalmol 2003;47:459–462** © 2003 Japanese Ophthalmological Society

**Key Words:** Disthyroid optic neuropathy, Graves' orbitopathy, pattern visual evoked potentials.

## Introduction

Disthyroid optic neuropathy (DON) is a serious complication of Graves' disease and it is due to direct compression of the nerve and/or blood supply at the apex of the orbit by swollen extraocular muscles. It develops in approximately 5% of all patients with Graves' orbitopathy (GrO) and sometimes can be detected only by subtle visual field and color vision defects. But most of the time, it is diagnosed after irreversible loss of visual function has occurred.[1] It has been noted that many times DON coincides with a congestive "active" phase of GrO. Diagnosis of DON at the subclinical stage may be obscured by the early external congestive symptoms and findings of the disease activity, but should be considered to be of utmost importance for early treatment.[1–3]

Pattern visual evoked potentials (P-VEP) shows electrical manifestation of brain response to an external stimulus. It has provided high sensitivity in the assessment of many central nervous system disorders, such as optic neuropathy. Electrophysiological abnormality is the most sensitive indicator of incipient optic neuropathy. The use of P-VEP has been demonstrated to be useful for early diagnosis of the optic nerve impairment in GrO.[4–7]

In this study, we tried to evaluate the efficacy of P-VEP in the detection of incipient involvement of the optic nerve in patients with GrO with no clinical symptoms or findings of optic neuropathy. Any possible correlation between P-VEP and the disease activity was also investigated in order to help understand the importance of "active" disease accompanying DON in the subclinical stage.

## Materials and Methods

P-VEPs obtained from 16 patients (32 eyes) with GrO were included in the study. Mean age of patients was

Received: November 13, 2003

Correspondence and reprint requests to: Gölge ACAROĞLU, MD, Angora Evleri, Masal Sokak, E 3/2, Beysukent, 06530, Ankara, Turkey. Tel.: 90 312 225 11 61; fax: +90 312 312 48 27 and +90 312 213 17 47; E-mail: golgetilki@yahoo.com

Jpn J Ophthalmol 47, 459–462 (2003)

Published by Elsevier Science Inc.

0021-5155/03/$–see front matter
doi:10.1016/S0021-5155(03)00101-1

Jpn J Ophthalmol
Vol 47: 459–462, 2003

41.7 ± 12.2 years (range, 20–65 years). Eleven patients were women and 5 were men. A normal control group consisted of 11 women and 4 men aged 23–65 years (mean = 42.3 ± 3.7 years). The study group included GrO patients being euthyroid for at least 3 months before the investigation, without any clinical or perimetric findings of glaucoma or optic neuropathy and having no signs of apical optic nerve compression on orbital coronal magnetic resonance (MR) images.

Exclusion criteria were evident optic neuropathy, severe myopia and astigmatism, cataract, glaucoma, maculopathy, best-corrected visual acuity below 20/25, and previous orbital radiotherapy.

All patients were given a complete ophthalmic examination, including visual acuity, color vision, evaluation of eyelid and soft tissue inflammation, ocular motility, Hertel exophthalmometry, biomicroscopic examination of the anterior segment, tonometry, and fundus examination. The computerized visual field examinations were done on the same day with the Humphrey Visual Field Analyzer HVF 630 (Allergan Humphrey, San Leandro, CA, USA), utilizing program 24-2, size III target, and standard background illumination of 31.5 apostilbs. Axial and coronal orbital MR imagings were performed with evaluation of optic nerve compression by apical crowding of the muscles.

P-VEP recordings were obtained using the standard settings of our clinic (stimulus number: 128, analysis period: 300 ms, band pass: 1.6–75 Hz) on a Medelec Neuropto device. The visual stimulus was a pattern-reversal checkerboard displayed on a 37-cm (14-inch) black-and-white monitor, placed at 1-m. distance from the patient. Check size of $16 \times 16$ mm$^2$ was chosen. The checkerboard had a 100% contrast and was alternated in time at 1 Hz with a space and time averaged mean luminance of 60 candela/m$^2$. Room lighting was kept constant during the examination (5 candela/m$^2$). Cortical responses were recorded using silver chloride electrodes placed over the occipital cortex 2 cm above the inion and referred to a midfrontal electrode with ground placed at the right mastoid. After optical correction with a pupillary diameter of 2 to 4 mm, monocular recordings were made. Over an analysis period of 300 milliseconds, signals were amplified 50,000 times and filtered to 1–100 Hz. Responses to 100 reversals were averaged. The P-100 component of the cortical response was considered for measurement. The time from stimulus reversal to the peak was calculated as the latency of P-100. P-100 latency values of patients were compared to those of the control group (Student's *t* test).

Each orbit was scored separately for the clinical activity of the disease using the scoring system proposed by Mourits et al,[8] shown in Table 1. The "Activity Score" is defined as the presence and degree of orbital signs and symptoms of inflammation. Any possible relationship between the P-100 latencies and the activity scores were analyzed using Spearman correlation analysis.

## Results

There was no significant difference between two groups for age and sex ($P > .05$). Exophthalmometry values ranged from 13 to 27 mm; and mean value was 21.3 ± 6.2 mm.

Mean P-VEP P-100 latency values of study and control groups are shown in Figure 1. Mean P-VEP P-100 latency values were significantly different in the GrO (122.0 ± 14.40 ms) and control groups (105.9 ± 7.7 ms) ($P = .0004$).

Activity scores of the GrO patients ranged from 0 to 5; mean activity score was 2.53 ± 1.5 according to the Activity Score system shown in Table 1. The GrO patients' P-100 latencies correlated mildly with their activity scores ($r = .364$; $P = .0406$) (Figure 2).

An example of one of the typical P-VEP's (patient's activity score was 5) showing delayed P-100 latency is shown in Figure 3.

## Discussion

Efficacy of P-VEP in the detection of incipient involvement of the optic nerve in patients with GrO with no

**Table 1.** Scoring System for Assessing the Activity of Graves' Orbitopathy*

| |
|---|
| Pain |
| Painful, oppressive feeling on or behind the globe |
| Pain on attempted up, down, or side gaze |
| Redness |
| Redness of the eyelid |
| Diffuse redness of the conjunctiva |
| Swelling |
| Chemosis |
| Swollen caruncle |
| Edema of the eyelid |
| Increase of proptosis of 2 mm or more during a period of time between 1 and 3 months |
| Impaired function |
| Decrease in visual activity of 1 or more lines on the Snellen chart (using a pinhole) during a period of time between 1 and 3 months |
| Decrease of eye movements in any direction equal to or more than 5 degrees during a period of time between 1 and 3 months |

*One point is given for each sign present; sum of these points is considered the "Activity Score".

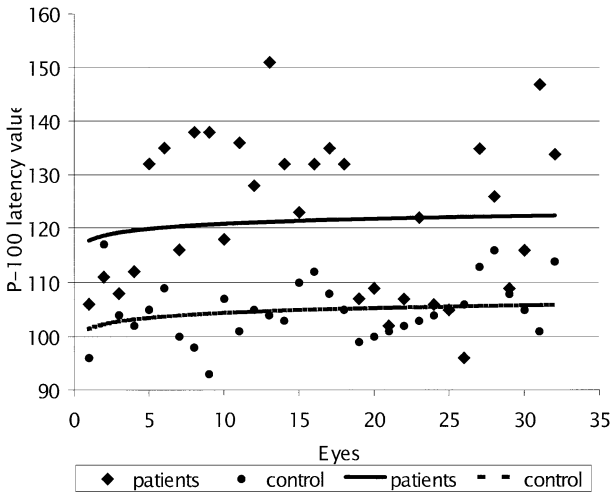


Figure 1. P-100 latency values and trend lines of patient and control groups.

clinical symptoms or findings of optic neuropathy, as well as any possible correlation between P-VEP and the disease activity were investigated in this study. It was demonstrated that mean P-VEP latencies of the GrO patients were significantly higher compared to normal controls. The disease activity scores of the patient group correlated mildly with the P-VEP P-100 latencies.

The proposed mechanisms for the physiopathology of GrO include toxic, mechanical, vascular, and ischemic factors.[1,3,8,9] The effect of mechanical factors is probably the most important.[9] Trokel and Jakobiec[10] clearly demonstrated that extraocular muscle thickening demonstrated by computerized tomographic scans, causing compression at the orbital apex correlated strongly with the severity of DON. In recent years several authors

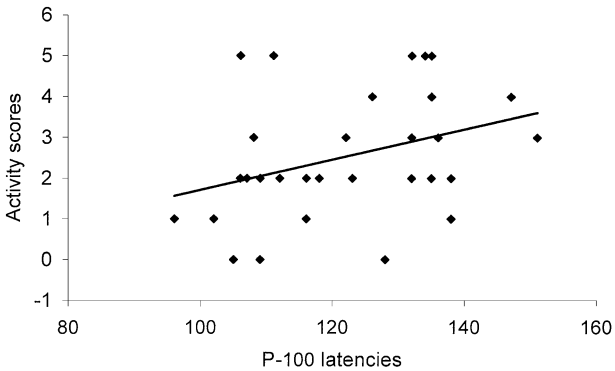


Figure 2. P-100 latency values and activity scores of the patients. A value of $R^2 = 0.1287$ indicates a mild correlation between the activity scores and P-100 latencies.

published cases of DON without apical compression.[11,12] Apart from the muscular pathology, extracellular edema in the orbital tissues leading to increased orbital pressure, and obstruction of the drainage of the superior orbital vein by the superior oblique-levator complex that inhabits a common fascial sheath may be possible mechanisms that cause DON.[12,13] These studies demonstrated the fact that the development of optic nerve compromise was not always associated with severe exophthalmos and/or apical compression. It was also a possible outcome of the disease activity; defined as the presence and degree of orbital signs and symptoms of inflammation.[8,11–13]

Electrophysiological studies are considered the most objective and sensitive methods of detecting early optic nerve abnormalities. Delay in P-100 latencies is a typical finding in optic nerve conduction disorders.[4,5,14] Latency of P-VEP increases with age especially after the fifth decade. In our study, patients' and control group's average ages were below 50. Disthyroidism also affects the P-VEP results. Hypothyroidism prolongs the latency of P-VEP, and treatment with L-T4 reverses the values to normal. All of our patients were euthyroid for at last 3 months before the examination. Thus, hypothyroidism or hyperthyroidism did not affect the results of P-VEP in this study.

Recent studies have shown that electrophysiological tests are useful tools in the diagnosis and monitoring of DON.[4–7,15] Batch and Lepre[4] found P-VEP to be valuable in the early diagnosis of DON. Tsaloumas et al[5] suggested the use of VEPs in monitoring of DON. More recently, Spaeda and colleagues[7] compared the P-ERG and P-VEP changes in GrO patients without clinical DON and concluded that both recordings appeared to be useful tools for early diagnosis of the optic nerve involvement. Genovesi-Ebert et al[15] found the P-ERG amplitude reduction to be the most sensitive parameter to demonstrate an early impairment of the optic nerve in GrO.

Our findings suggest that P-100 latencies may be significantly delayed in GrO patients, even without any clinical signs of DON; a similar result was obtained in Salvi et al's[6] study. Salvi et al found no correlation between inflammatory activity and P-100 latencies, but we found that the magnitude of this delay mildly correlated with the activity of orbital inflammation. This implies that the orbital inflammatory response may adversely affect the optic nerve conduction.

On the basis of these findings, we conclude that the optic nerve may be subclinically involved in patients with GrO. DON may be preceded by active signs of inflammation even in the absence of apical compression. The important implication is that the inflammation can be

Jpn J Ophthalmol
Vol 47: 459–462, 2003

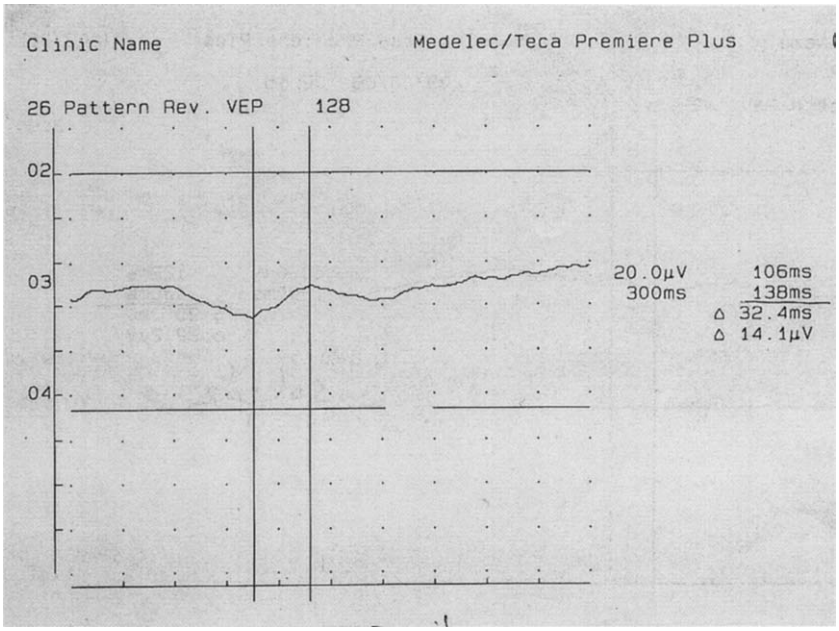


Figure 3. Example of one of the typical pattern visual evoked potentials (P-VEP; patient's activity score was 5) showing delayed P-100 latency.

controlled by medical therapy before DON develops clinically. Therefore, the use of P-VEP is valuable in monitoring patients with ''active'' congestive disease.

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