# Visual Evoked Potentials (VEP) in Graves' Disease Patients in Siriraj Hospital

**Atiporn Thuangtong, M.D.*, Chonlada Wangvarunyoo, M.D.*, Tada Kunavisarut, M.D.**, Nitinun Phithakphaosakul, B.Sc.***
**Department of Ophthalmology, **Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

## ABSTRACT

**Objective:** To evaluate the visual evoked potentials (VEP) in Graves' disease patients in order to reveal the possible presentation of subclinical optic neuropathy.
**Methods:** Forty-seven Graves' disease patients without symptoms of optic neuropathy were enrolled. Flash visual evoked potentials (F-VEP) and Pattern visual evoked potentials (P-VEP) were evaluated. Comparison of VEP with normal values was done, between the groups with and without the presentation of eye sign(s) and also among the groups that had differences in thyroid hormone function.
**Results:** The mean F-VEP amplitude and latency were 17.56±6.20 microvolts (μV) and 114.02±14.92 milliseconds (ms), respectively. The mean P-VEP amplitude and latency were 10.82±4.88 μV and 99.67±5.87 ms, respectively. These values were within normal values. Only the latency of P-VEP was increased significantly (P<0.001) when compared between the groups with (101.81±5.70 ms) and without eye signs (97.43±5.21ms) and it also increased significantly (P=0.033) when compared with normal values. The hyperthyroid group also had a significant increase in the latency of P-VEP when compared to other groups (P=0.002).
**Conclusion:** Increase in the latency of P-VEP should be sought for and reminded the clinician to conduct close follow-up of this as an early sign of optic neuropathy, especially in the patients with eye manifestation.

**Keywords:** Visual evoked potentials, Graves' disease, subclinical optic neuropathy

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## INTRODUCTION

Graves' disease is a relatively common autoimmune disorder. Thyroid-associated ophthalmopathy (TAO) is indicated when a Graves' disease patient has any eye manifestation(s) that are characterized by edema and infiltration of the extraocular muscles and orbital tissue[1]. The disease has variable clinical presentations and may cause severe damage to vision and orbital architecture. Eyelid retraction is the most common eye manifestation (56%) follow by soft tissue involvement (38%), proptosis (16%), restrictive myopathy (11%) and optic neuropathy (7%).[2]

Even though the optic neuropathy develops only in a small number of patients, it is the most serious complication and can cause permanent visual loss if the treatment is delayed. The optic neuropathy is caused by an increase of muscle volume compressing on the optic nerve and its blood supply at the orbital apex. The clinical symptoms and signs of compressive optic neuropathy may present with either a sudden or progressive decrease in visual acuity, color vision impairment and/or visual field defect.

The visual evoked potential (VEP) is an electrical manifestation of brain response to an external stimulus; it is used to assess many disorders of the central nervous system and compressive lesion of anterior visual pathway.[3] Many studies[4-10] found that VEP can identify an early stage of optic neuropathy in Graves' disease patients in the absence of decreased visual acuity.

The aim of this study was to evaluate the VEP values in Graves' disease patients and to compare with the normal VEP values in Siriraj Hospital's Electrophysiologic laboratory to reveal the possible presentation of subclinical optic neuropathy.

## MATERIALS AND METHODS

Graves' disease patients were recruited from July 2010 to December 2011. All of the patients signed the consent form of the study protocol which was approved

*Correspondence to: Atiporn Thuangtong*
*E-mail: atipornpam@yahoo.com*
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by the research ethics committee of Siriraj Hospital, Mahidol University. Only Graves's disease patients that were 18 years old and older showed no symptoms and signs of optic neuropathy, and had no known systemic or ocular condition that might affect the results of VEP were included.

Demographic data (age, sex), medical history, including time since Graves' disease was diagnosed, symptoms of hyperthyroidism, any past ocular symptoms, status of thyroid hormone, medication taken, smoking history and family history of thyroid disease were recorded.

All the patients underwent complete eye examination. The best-corrected visual acuity, color vision and intraocular pressure were measured. Hertel's exophthalmometer was used to determine the degree of proptosis. Palpebral fissure width and levator function were measured. Strabismus examination was done using Hirschberg's test, alternate cover test and measurement of the degree of eye movement. Slit-lamp biomicroscopy of the anterior segment and optic disc was done. Any "eye signs" that were seen in Graves' disease patients were recorded. Humphrey perimetry was done after complete eye examination.

VEP was performed according to the standard VEP record which was established by the International Society for Clinical Electrophysiology of Vision (ISCEV)[11] using 2 types of stimulus for VEP response: flash stimulus (F-VEP) and pattern reversal (full field checkerboards subtending 15 minutes of arc) stimulus (P-VEP). This study used cut point values of Siriraj Hospital's Electrophysiologic laboratory values as follows: F-VEP amplitude = 10 microvolts (μV), F-VEP latency = 120 milliseconds (ms), P-VEP amplitude = 5μV and P-VEP latency = 100 ms.

Quantitative data was described as mean and standard deviation (SD). Number and percentage were used to describe qualitative data. Mann-Whitney U test or unpaired t-test was used to compare the difference between two groups as appropriate. One way ANOVA was used to compare the mean among three groups; multiple comparisons were made by Games-Howell whereas Kruskal-Wallis test was used to compare the mean among the three groups follow by multiple comparisons using Bonferroni adjusted significance level as appropriate. The data were analyzed using PASW statistics 18.0 (SPSS). All tests of significance were two tailed with a p-value less than 0.05 considered statistically significant.

## RESULTS

Forty-seven patients (92 eyes) with Graves' disease consisted of 6 men and 41 women. All of them had normal in their color vision test and visual field test in both eyes. The mean intraocular pressure was 14.13±2.65 mm Hg. Demographic data of the patients has been shown in Table 1. There were 24 patients that had thyroid-associated ophthalmopathy (TAO). Eyelid retraction (83.33%) was also the most common eye manifestation follow by soft tissue involvement (33.33%), proptosis (33.3%) and restrictive myopathy (20.83%).

The mean amplitude and latency of F-VEP and P-VEP of Graves' disease patients have been shown in Table 2. The patients were separated into 2 groups: with TAO and without TAO. The mean amplitude and latency of F-VEP and P-VEP of each group have been compared (Table 2).

All of these values from overall of Graves' disease patients were within the normal values of our lab. Only the latency of P-VEP of the group with TAO (101.81±5.70 ms) increased significantly ($p<0.001$) when compared with the group without TAO (97.43±5.21 ms). When comparing these values (101.81±5.70 ms) with normal values, we found that they had increased significantly ($p=0.033$) when compared to the normal values with a mean difference of 1.810 ms.

Then we grouped the patients according to the thyroid hormone function as group 1 (n= 15): euthyroid,

**TABLE 1.** Demographic data of the patients.

| | Overall (n=47) | With TAO (n=24) | Without TAO (n=23) | p-value |
|---|---|---|---|---|
| Age (yr) | | | | |
| Mean±SD | 42.7±13.48 | 42.2±15.36 | 43.3±11.33 | 0.880 |
| Length of Graves' disease(yr) | | | | |
| Mean±SD | 5.3±6.20 | 4.6±4.90 | 6.0±7.30 | 0.627 |
| Gender | | | | |
| Male | 6 (12.8%) | 4 (16.7%) | 2 (8.7%) | 0.199 |

TAO = Thyroid-associated ophthalmopathy

**TABLE 2.** The mean amplitude and latency of F-VEP and P-VEP of Grave's disease patients.

| Mean VEP values | Overall | With TAO | Without TAO | p-values |
|---|---|---|---|---|
| F-VEP amplitude (μV±SD) | 17.56±6.20 | 18.09±7.69 | 17.00±4.14 | 0.883 |
| F-VEP latency (ms±SD) | 114.02±14.92 | 116.45±17.40 | 111.48±11.42 | 0.248 |
| P-VEP amplitude (μV±SD) | 10.83±4.88 | 11.62±6.03 | 10.00±3.14 | 0.360 |
| P-VEP latency (ms±SD) | 99.67±5.87 | 101.81±5.70 | 97.43±5.21 | <0.001** |

F-VEP=Flash visual evoked potential, P-VEP=Pattern visual evoked potential, μV=microvoltage, ms=millisecond, TAO=Thyroid-associated ophthalmopathy
**significant at 0.001 level

**TABLE 3.** The mean amplitude and latency of F-VEP and P-VEP in the group with euthyroid, hypothyroid and hyperthyroid.

| Mean VEP values | Euthyroid group | Hypothyroid group | Hyperthyroid group | p-values |
|---|---|---|---|---|
| F-VEP amplitude (μV±SD) | 17.09±5.21 | 17.63±7.10 | 17.89±6.40 | 0.743 |
| F-VEP latency (ms±SD) | 115.23±14.89 | 118.38±17.33 | 110.08±12.34 | 0.096 |
| P-VEP amplitude (μV±SD) | 9.10±3.09 | 11.22±5.30 | 11.93±5.44 | 0.051 |
| P-VEP latency (ms±SD) | 98.40±6.98 | 97.50±4.23 | 102.16±5.03 | 0.002* |

F-VEP=Flash visual evoked potential, P-VEP=Pattern visual evoked potential, μV=microvoltage, ms=millisecond
*significant at 0.05 level

group 2 (n=13): hypothyroid and group 3 (n=19): hyperthyroid and then compared the mean amplitude and latency of both F-VEP and P-VEP among the groups. (Table 3)

Only the latency of P-VEP was significantly different (p=0.002) among the three groups. A multiple comparison test was used to analyze them and it was found that the latency of P-VEP of the hyperthyroid group was increased significantly from the hypothyroid and euthyroid groups, but there was no significant difference of the latency of P-VEP in the euthyroid and hypothyroid groups. When compared to the normal values, the latency of P-VEP in the hyperthyroid group was also increased significantly from normal values (p=0.012) with a mean difference of 2.158 ms.

## DISCUSSION

The optic neuropathy in TAO is caused by compression of the optic nerve at the orbital apex from the enlarged extraocular muscles[12]. Decreased visual acuity, color vision impairment, visual field defect, relative afferent pupillary defect and optic nerve head swelling are symptoms and signs that are found in patients with optic nerve compression. Marked proptosis, palpable lacrimal gland, increase in intraocular pressure on up gazing and restriction of extraocular movement are predictors for optic nerve compression[13]. With this study, all of the patients had no symptoms and signs of optic neuropathy and all of the values (amplitude of F-VEP, latency of F-VEP, amplitude of P-VEP and latency of P-VEP) were within the normal values of our Electrophysiological laboratory in contrast to many previous studies[4-9] that found an increase in the latency of P-VEP even in asymptomatic optic neuropathy. The difference between our study and the previous studies was the inclusion criteria that in this study we included all of the Graves' disease patients, both those with and those without TAO. After grouping the patients according to the presentation of TAO, the result was the same as mentioned by previous studies in that the latency of P-VEP of the group that had TAO was increased significantly when compared with the group that had no TAO and was also increased significantly when compared with the normal values even though all of the patients with TAO had no signs and symptoms of optic neuropathy. The latency of P-VEP which increased was not as much as the increasing of latency of P-VEP that is seen in demyelinating diseases. Wijngaarde et al.,[9] explained the pathophysiology of this as a demyelinating-like neuritis which causes impaired optic nerve conduction. Halliday et al.,[14] suggested that the delay in VEP response was smaller and less frequent in patients with compressive lesion compared to patients with demyelinating disease. Ambrosio et al.,[15] found that an increase of P100 latency was not helpful for the differential diagnosis between eyes with dysthyroid optic neuropathy and eyes with Graves' ophthalmopathy and ocular hypertension or glaucoma. Reduction in N75-P100 amplitude for 15' of visual angle of pattern stimulation from compressive damage was considered in the differential diagnosis from glaucomatous damage of the optic nerve in patients with graves' ophthalmopathy.

For the patients with a difference in thyroid hormone function, hypothyroidism has been reported to prolong the latency of pattern VEP.[16-18] Salvi et al.,[4] found that the patients with euthyroid or hypothyroid were not affected by the results of the VEP test. Mitchell et al.,[19] found no significant change in pattern VEP response in hyperthyroid patients. In this study, it was found that the latency of P-VEP was significantly increased in the hyperthyroid group, thus differing from those in the euthyroid and hypothyroid groups, and it also increased more than normal values. Hyperthyroidism and TAO are close involved in clinical and temporal relationships which evolve from a single underlying systemic process with variable expressions. Almost half of the patients with Graves' hyperthyroidism report symptoms of TAO[20], thus the patients with hyperthyroidism may be prone to have optic neuropathy more than the patients with hypothyroidism and euthyroidism.

In conclusion, this study has shown that P-VEP may indicate an optic neuropathy even in asymptomatic optic nerve dysfunction. Increase in the latency of P-VEP should be looked for and clinicians reminded to conduct close follow-up for early signs of optic neuropathy, especially in patients with eye manifestation.

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