The Study of Visual Evoked Potentials in Children and Young Patients with Autoimmune Thyroid Disease

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Introduction. 20-25 percent of patients with autoimmune thyroid disease – Graves' disease (GD), have clinically obvious Graves' ophthalmopathy, while only 3-5% will develop severe ophthalmopathy. Graves' ophthalmopathy (GO) is an autoimmune inflammatory disorder affecting the orbit and characterized by upper eyelid retraction, lid lag, swelling, redness (erythema), conjunctivitis, and proptosis. The most serious complication in Graves' ophthalmopathy – optic neuropathy (ON) could appear due to compression of the optic nerve at the orbital apex by the swollen extraocular muscles to proliferation of retrobulbar fat and connective tissue. Unfortunately, these symptoms and signs of ON are not always present, and the patient may be unaware of visual loss until advanced clinical changes have occurred. Electrophysiological investigations, such as visual evoked potentials (VEP), are considered the most objective and sensitive method of detecting early optic nerve abnormalities in patients with Graves' disease.

Materials and methods. In present case-control study we assessed 98 (196 eyes) patients with Graves' disease (case group) and 34 (68 eyes) age-matched normal subjects (control group). Inclusion criteria for patients group were: from 6 to 35 years old; with diagnosis of Graves' disease; no known other ophthalmic, neurological diseases that might affect the results of the study. 34 (68 eyes) – aged from 7 to 35 years old, healthy subjects without known ophthalmic, endocrine and neurological diseases were studied as controls. The study was approved by Lithuanian Bioethics Committee. Written informed consent was obtained from all participants or their parents. The participants were subdivided in three groups according the age: ≤13years old (group1); 14-18 years old years old (group 2); ≥19 years old (group 3).

The diagnosis of thyroid disease was based on clinical signs and laboratory thyroid function testing. We recorded patient's data: age, sex, family history (thyroid disorders). Ophthalmological examination included best-corrected Snellen visual acuity, the amount of proptosis by digital image processing system consisting of Hertel's exophthalmometer, video camera and personal computer [1], slit lamp examination and funduscopy and tonometry (Schiotz tonometer). GO activity and severity were assessed according to the EUGOGO (European Group on Graves' Orbitopathy) recommendations. The patients with a clinical activity score (CAS) ≥3/7 were considered as having active GO.

We have recorded visual evoked cortical potentials with RETI port 32, Roland Consult, according to the standard VEP record which was established by International Society for Clinical Electrofisiology of Vision (ISCEV), using pattern reversal stimulus for VEP response. Pattern-reversal VEPs elicited by checkerboard stimuli with large 1° (60 min of arc) and small 0.25° (15 min) checks [2].

The visual stimulus was displayed on a black and white monitor placed 1.0 meter from the patient. The mean luminance of the checkerboard was 60 candela/m² and contrast between black and white squares of the checkerboard was 100%. Cortical responses were recorded from an electrode placed 2 cm above the inion (over the visual cortex), referenced to a midfrontal electrode, with ground placed at the forehead. We used gold disc skin electrodes. Impedance was kept below 5 kΩ. Monocular stimulation was adopted in all investigations with best corrected vision. They were instructed to fixate red dot located in the centre of monitor (15" Samsung CRT monitor SyncMaster 551s). We analysed the latency of P100 and amplitude of P100 from the preceding N75 peak from the subject's reports. Statistical analysis was conducted using statistical SPSS software package (Version 19.0).

Results. We analysed 98 subjects (196 eyes) in patients group (group 1) with Graves' disease diagnosis. The mean age in was 23.65±8.2, ranged from 6 to 35 years old. The control group was consisted of 34 (68 eyes) healthy participants, aged from 7 to 35 years old. The mean age in controls was 20.76±8.23. We subdivided patients and control subjects eyes in 3 subgroup depended on age.

Table 1. Demographic data of patients Graves' disease

Patients	**1 group (≤13 years)**	**2 group (14-18 years)**	**3 group (≥19 years)**
Number of eyes	20	38	138
Mean age (years) Mean±SD	9.6 ± 2.48	16.0 ± 1.06	27.8±5.68
Median duration of the disease (months) Mean±SD	1.3±0.4	9.39±18.09	10.3±19.43
Female/Male (%)	100/0	84,2 / 15.8	89.9/10.1

Table 2. Demographic data of control group

Controls	**1 group (≤13 years)**	**2 group (14-18 years)**	**3 group (≥19 years)**
Number of eyes	22	10	36
Mean age (years) Mean±SD	11.4 ± 1.81	16.0 ± 0.94	27.8 ± 3.72
Female/Male (%)	72.7 / 27.3	80.0 / 20.0	61.1/38.9

Comparing results in the age group I (≤13 years) between patients and control groups, we found, that the latency P100 increased significantly ($p<0.05$) of the patients group to stimulus of 1º, and 15'. Regarding amplitude – there was

significantly larger amplitudes for the peak to peak N75-P100 response for both 1º and 15' stimulus in the patients group (Table 3).

According to the comparing results in the age group II (14-18 years) between patients and control groups (Table 4), we found significantly higher VEP amplitudes and prolonged latencies P100 in patients group for 1º and 15'stimulus).

Table 3. Data of patients Graves' disease and control group I, aged ≤13 years old

	Patients Mean ±SD	**Controls Mean ±SD**	**p-values**
Mean age (years)	9.6± 2.48	10.36±1.81	0.106
Latency P100, 1º (ms)	107.40±7.49	101.54±3.29	0.026
Latency P100, 15' (ms)	114.35±8.34	108.95±6.28	0.029
Amplitude, N75-P100, 1º(μV)	11.08± 5.61	7.27±1.92	0.002
Amplitude, N75- P100,15'(μV)	11.42± 6.20	6.66±1.44	0.011
Visus	0.89±0.32	1.00±.00	0.001
Proptosis (mm)	16.61± 2.89	14.78±1.22	0.001
Valid N (listwise)	20	22	

*ms - milliseconds, μV – microvoltage, mm – millimeters
**Significant at 0.05 level

Table 4. Data of patients Graves' disease and control group II, aged 14-18 years old

	Patients Mean ±SD	**Controls Mean ±SD**	**p-values**
Mean age (years)	15.95±1.06	16.00±0.94	0.832
Latency P100, 1º (ms)	101.71±4.10	100.40±3.13	0.049
Latency P100, 15' (ms)	112.73±5.12	111.30±7.36	0.053
Amplitude, N75-P100, 1º(μV)	10.21±6.19	4.82±0.83	0.001
Amplitude N75- P100,15'(μV)	10.40±5.52	4.77±1.63	0.001
Visus	0.97±0.17	1.00±0,00	0.001
Proptosis (mm)	16.76±1.77	13.71±1.25	0.001
Valid N (listwise)	38	10	

*ms - milliseconds, μV – microvoltage, mm – millimeters.
**Significant at 0.05 level.

We distinguished significantly prolonged VEP latency P100 for 1º and 15' in the age group III (≥19 years old) comparing results between patients and control groups (Table 5). The amplitude was not significantly different between groups. The visual acuity was significantly lower in patients with Graves' disease group comparing with control in whole ages subgroups. The mean proptosis was enlarged in each age groups comparing Graves' disease patients to healthy persons (Tables 3-5).

Table 5. Data of patients Graves' disease and control group III, aged ≥19years old

	Patients Mean ±SD	**Controls Mean ±SD**	**p-values**
Mean age (years)	27.81± 5.68	27.83±3.72	0.715
Latency P100, 1º (ms)	102.88±6.44	100.92±5.37	0.022
Latency P100, 15' (ms)	110.55±8.91	109.03±7.33	0.007
Amplitude, N75-P100, 1º(μV)	7.94±5.19	4.96±2.08	0.076
Amplitude N75- P100,15'(μV)	7.72±4.77	5.02±2.55	0.082
Visus	0.92±0.27649	1.00±0.00	0.001
Proptosis (mm)	17.60±2.94	14.86±2.53	0.001
Valid N (listwise)	138	36	

*ms - milliseconds, μV – microvoltage, mm – millimeters.

**Significant at 0.05 level.

Discussion. Ocular changes are rare in children with thyroid diseases and this is the largest and the first study of assessment of eye disorders and visual evoked cortical responses in children and young adults with thyroid diseases in Lithuania. A.I. Gogakos et al. (2010), G.E. Krassas et al. (2007) showed that eye clinical picture in children is less well defined than in adults [3, 4]. VEP testing may be helpful to assess the optic nerve impairment in incipient ON in cases of Graves' disease. Existing reports of VEP studies in Graves' disease are not consistent because of the different techniques used.In present study we found higher latency of P100 for 1º and 15'of the evoked cortical response recorded in all patients groups without clinical ON, there was found statistically different visual acuity between patients and control group. The increased latency of visual evoked cortical responses in adult patients with Graves' disease noted A. Thuangtong et al. (2013) [5]. In adult patients with Graves' ophthalmopathy the prolonged latency of VEP without subjective visual complains and without optic nerve compression showed M.Salvi et al. (1997) [6]. Authors believe that the study of VEP in Graves' ophthalmopathy is complementary to the others studies in identifying early optic nerve dysfunction in the absence of decreased visual acuity. G. Ambrosio et al., (2003) in showed that disturbances of VEP were found mainly in patients with Graves' ophthalmopathy complicated by optic neuropathy [7].

We have found signifficant higher amplitudes N75-P100 in patients with GD in children and adolescens groups. We did not find studies in medical literature of visual evoked potentials in children with Graves' disease, perhaps due to the fact that pediatric Graves' disease is very rare and we cannot compare our data with other pediatric studies [8]. We have found high amplitude values in few pediatric patients with Graves' disease. We still have no explanation for these findings. Investigators have suggested that hormonal differences may play a major role in accounting for VEP sex differences. In (Dion LA 2013) study was found, that school age girls had signifficant large amplitudes than boys [9]. The

values of proptosis in patients group were statistically higher than in control in present study in all age groups.

Conclusions. This study shows that visual evoked cortical responses detect visual function abnormalities noninvasively in children and young adults with Graves' disease. VEP to pattern stimulation is sensitive objective method to predict visual impairment in Graves' optic neuropathy. This examination may be useful in early diagnosis of ocular changes in children and young adults with autoimmune thyroid diseases.

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The aim of the study was to investigate the clinical potential for the visual evoked potentials (VEP) among the groups of adolescents and young patients with autoimmune thyroid disease (ATD) without clinical signs of optic neuropathy. The VEP were obtained for 98 (196eyes) ATD patients (group I) and age-matched normal subjects 34 (68 eyes) without ATD. This study shows that visual evoked cortical responses detect visual function abnormalities noninvasively in children and young adults with Graves' disease. VEP to pattern stimulation is sensitive objective method to predict visual impairment in Graves' optic neuropathy. This examination may be useful in early diagnosis of ocular changes in children and young adults with autoimmune thyroid diseases.