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Visual Evoked Potential Can Be Used to Detect a Prediabetic Form of Diabetic Retinopathy in Patients with Diabetes Mellitus Type I

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A B S T R A C T

The aim of this study was to evaluate the usefulness of visual evoked potential (VEP) testing in detecting retinal ganglion cell damage in patients with Diabetes Mellitus type I (DMI). VEP arise before diabetic retinopathy signs become ophthalmoscopically detectable. VEP testing was performed in 45 patients divided into three groups; 15 children with recently discovered DMI, 15 children with long-lasting DMI, and 15 healthy children as the control group. A statistically significant difference in VEP P100 wave amplitudes ($Z=4.02$, $p<0.001$) and latencies ($Z=-4.66$, $p<0.001$) was found between children with established DMI and those with recently discovered DMI. Amplitude values decrease progressively and latency values increase progressively in children with DMI as the years pass. Progressive increases in VEP latency values are a direct sign of retinal ganglion cell damage, which takes place even before the first ophthalmoscopically detectable signs of diabetic retinopathy arise. Therefore, VEP should be considered as a valid method for detecting prediabetic retinopathy, which could contribute greatly to the prevention of diabetic retinopathy complications.

Key words: *evoked potentials, visual, Diabetes Mellitus type I, diabetic retinopathy, human, controlled clinical trials, Croatia*

Introduction

Type I Diabetes Mellitus (DMI) is a complex, polygenic, self-destructive disease that has many possible etiological factors. Chronic complications of DM1 are mostly caused by blood vessel damage. The most frequent chronic microvascular complications usually become clinically evident in early adulthood, but they can also be seen in the pediatric population. Fortunately, chronic microvascular complications, such as cerebrovascular stroke, cardiovascular diseases, and peripheral vascular disease of the limbs, are very rare during puberty and adolescence. Due to recent improvements in diagnostic procedures, we have been able to detect even subclinical pathological changes in children and adolescents.

Diabetic retinopathy is the leading cause of blindness among patients between the ages of 20 and 65 years old (the working population) in developed countries. Blindness was absent from 86% of eyes among diabetic patients under 25 years old. According to the international clinical classification of diabetic retinopathy, there are three different stages: diabetic preretinopathy, nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy.

Diabetic retinopathy is a manifestation of generalized microangiopathy typically found in diabetics. Biochemical and cellular mechanisms that induce vascular and extravascular lesions are complex and still partially unknown. Chronic hyperglycemia is one certain cause of diabetic retinopathy. To date, there are four described pathobiochemical mechanisms that underlie hyperglycemic blood vessel damage: aldol reductase activity, protein kinase C activation, high levels of glycosylated compounds, and free oxygen radical production.

Ophthalmologic electrodiagnostic findings allow us to localize the damaged part of the visual path. Diabetic

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retinopathy involves all retinal layers. Electroretinogram (ERG) and visual evoked potential (VEP) findings reflect the grade of organic damage. In early-stage diabetes, ERG reveal changes in »b« waves; in late-stage diabetes, there are some changes in »a« waves too. Multiple previous studies showed that VEP findings may identify pathology in both early- and late-stage diabetes. The sensitivity of neurophysiological examinations permits the detection of retinal dysfunction, even before clinical manifestations develop and while visual acuity is still normal. According to previously cited literature, damage of retinal ganglion cells may occur even before vascular lesions become clinically visible. Our hypothesis was that there is a direct correlation between ischemic ganglion cell changes and VEP parameters. The aim of this study was to determine the role of VEP testing in evaluation of ganglion cell damage, which is a sign of diabetic preretinopathy.

Materials and Methods

This study included 45 patients, who were divided into 3 study groups of 15 patients each. The first group consisted of children who were 9 to 12 years old with recently diagnosed DMI. The second group consisted of patients who were 9 to 12 years old, who had been treated for DMI for years. The last was the control group, which consisted of healthy children who were 9 to 12 years old.

All patients were submitted to endocrinological and ophthalmological examination, which included examination of visual acuity, direct ophthalmoscopy on dilated pupils, VEP testing (Primus-Tomey) with a square-pattern stimulus with space frequency of 73.20 min., time frequency of 1 rps, contrast 99%, time of acquisition 300 ms. Each eye was tested separately. The fundus photograph was obtained using the Zeiss FF 450 plus fundus camera. Examinations were performed at the Eye Clinic Outpatients Department and at the Pediatric Endocrinology Department of Split University Hospital, Croatia.

Good regulation of blood glucose levels was the inclusion criteria for all patients. Informed consent was obtained from one parent of each child. Statistical analysis was performed with Statistica 6.0 software (StatSoft Inc.). Differences between groups were analyzed with the Kruskal-Wallis test, Mann-Whitney U-test and Wilcoxon matched-pair test. Pearson's correlation coefficient was calculated to determine the correlation between variables.

Results

All examined patients had normal eye fundus findings. Most important demographic and other characteristics of the three examined groups are listed in Table 1.

No statistically significant difference was found between values of measured amplitudes and latencies in the eyes of each of the three groups (Table 2); therefore, further calculations were all calculated using mean values that considered both right and left eyes.

Statistical analysis showed that there was a significant difference among the three groups in P100 wave amplitude (Kruskal-Wallis test, $H=22.69$, $p<0.001$) (Figure 1). Further analysis showed that there was a very significant difference between the amplitude values of children with established DM1 and the control group (Mann-Whitney U-test, $Z=4.17$, $p<0.001$). No difference

TABLE 1
DEMOGRAPHIC DATA FOR THE THREE STUDY GROUPS

Study group	Children with recently discovered diabetes type 1	Children with established diabetes type 1	Control group
Number of patients	15	15	15
Gender (M/F)	9/6	7/8	10/5
Age median (range)	10 (9–13)	19 (18–21)	10 (9–13)
Median duration of diabetes in years (range)	–	8 (7–10)	–

TABLE 2
COMPARISON OF RIGHT- AND LEFT-EYE P100 WAVE AMPLITUDES AND LATENCIES AS MEASURED IN ALL THREE STUDY GROUPS

		Right eye Δ (range)	Left eye Δ (range)	p-value*
Children with recently discovered diabetes type 1	Amplitude	11.10 (9.8–12.1)	11.3 (9.7–12.2)	0.9171
	Latency	105.9 (103.8–106.1)	105.9 (103.8–106.1)	1.0000
Children with established diabetes type 1	Amplitude	9.8 (8.7–11.0)	9.6 (8.6–11.1)	0.9503
	Latency	110.9 (109.8–111.7)	110.9 (109.8–111.7)	0.9336
Control group	Amplitude	11.3 (9.9–12.5)	11.4 (9.5–12.1)	0.9334
	Latency	106.0 (103.9–106.1)	106.00 (103.9–106.1)	0.8642

*Mann-Whitney U-test

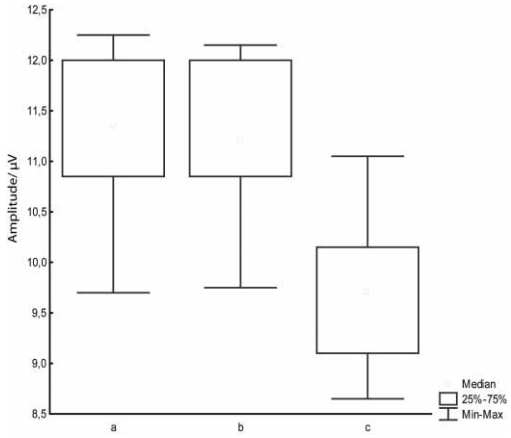

Fig. 1. P100 wave amplitude median and range in three study groups (a=Control group, b=Children with recently discovered diabetes mellitus type 1, c=Children with established Diabetes Mellitus Type I).

was found between recently discovered diabetic children and the control group (Mann-Whitney U-test, Z=0.18, p=0.85).

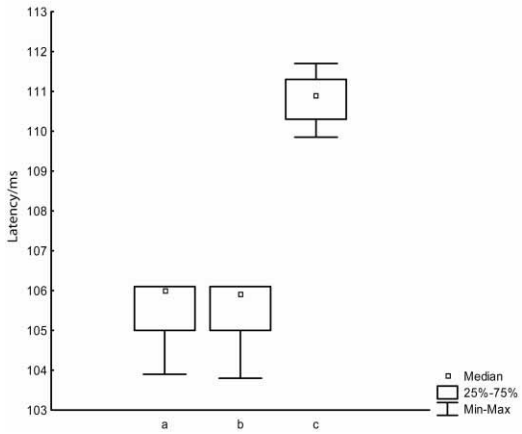

Fig. 2. P100 wave latency medians and ranges in all three study groups (a=Control group, b=Children with recently discovered diabetes mellitus type 1, c=Children with established Diabetes Mellitus Type I).

Statistical analysis of the P100 wave latencies showed similar results. There was also a significant difference in P100 wave latencies among the three examined groups (Kruskal-Wallis test, H=29.74, p<0.001) (Figure 2). Further analysis demonstrated again a significant difference between the latencies of children with established DMI and the control group (Mann-Whitney U-test, Z= –4.66, p<0.001), but once more, no difference was found between children recently diagnosed with diabetes and the control group (Mann-Whitney U-test, Z=0.39, p= 0.69). We found a weak negative correlation between the number of years a patient has lived with diabetes and P100 wave amplitude (Pearson's correlation coefficient, R= –0.07). A somewhat more significant negative correlation was found between the number of years a patient had lived with diabetes and latency values (Pearson's correlation coefficient, R=–0.18).

P100 wave amplitudes in the group with recently discovered DMI were significantly different from the amplitudes in the group with established DMI (Mann-Whitney U-test, Z=4.02, p<0.001). Lower amplitude values were associated with increased age among diabetic patients (Figure 3). Significant difference in P100 wave latencies were also found between the same groups (Mann-Whitney U-test, Z=–4.66, p<0.001), but latency values had the tendency to increase with patient age (Figure 4).

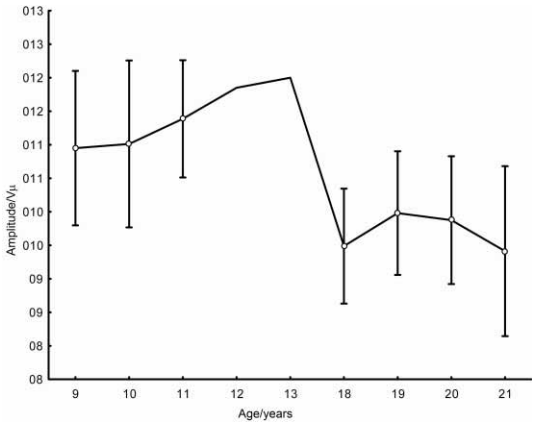

Fig. 3. Relation between age and P100 wave amplitude values in patients with Diabetes Mellitus Type I.

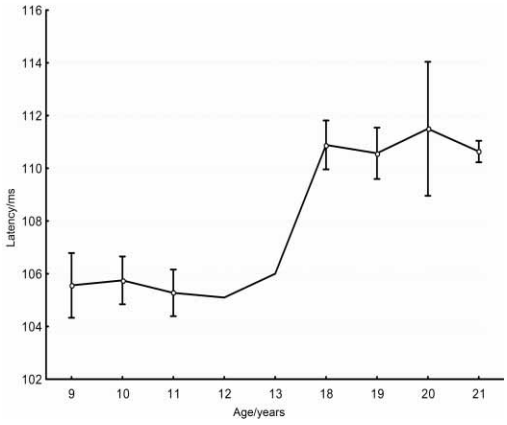

Fig. 4. Relation between age and P100 wave latency values in patients with Diabetes Mellitus Type I.

Discussion

Electroretinogram (ERG) is an important electrodiagnostic procedure, which detects diffuse retinal changes. ERG findings become pathological only if a large part of the retina is damaged because ERG represent the response of photoreceptors and Müller cells. Diabetic retinopathy is ophthalmoscopically detectable because it involves all retinal layers; therefore, ERG findings are also pathological. The VEP represents cortical responses

upon visual stimulation and can also be used to evaluate the visual path, which runs from retinal ganglion cells to the visual cortex. Latency is retained as the most objective VEP parameter; amplitude is less reliable due to its greater variability. Therefore, this paper focused more on the correlation of latency values among the three groups examined and the duration of diabetes. Vascular damage in diabetic retinopathy is caused by products of non-enzymatic glycosylation; this evidence in combination with retinal-specific neural transport theory suggests that the etiology of diabetic retinopathy is not exclusively vascular; retinal ganglion cell damage theory suggests that retinal function may be damaged even before vascular lesions arise. We found no statistically significant correlation between diabetes duration and P100 wave latency and amplitude, which indicates that ischemic neuronal and other retinal structure damage generated by microangiopathy is the major but not the only cause of neurophysiologic changes.

Extracellular glutamate accumulation in diabetes indicates that retinal ganglion cell damage is caused by glutamine excitotoxicity. Functional and anatomical changes can arise even before vascular lesions. Color perception dysfunction (decreased blue-yellow sensitivity) and ERG changes (b-wave amplitude reduction) favor this theory. Oxidative stress, apart from functional microcirculation abnormalities and physiologic consequences of glucose metabolism, has a significant role in the pathogenesis of diabetic retinopathy. Oxidative stress arises due to increased free radical and oxidant production or diminished activity of antioxidative mechanisms.

No statistically significant difference in amplitude and latency values was found between the group of children recently discovered to be diabetic and the control group, which indicates that there is no retinal ganglion cell damage in patients with recently discovered DMI. Differences in P100 wave amplitudes and latencies between the group of children with established DMI and the control group indicate that VEP, as electrodiagnostic examination method, detected retinal ganglion cell damage in the second group. This ganglion cell damage can be defined as a sign of preclinical diabetic retinopathy because no examined patients had ophthalmoscopically detectable signs of diabetic retinopathy. These results favor the neurogenic diabetic retinopathy development theory, which states that P100 wave latency changes even before the first clinical signs of eye fundus arise. We also noticed a progressive decrease in P100 wave amplitude values with increasing age among diabetic children, but amplitude decreased with age in the general population (Figure 3). Latency values, in patients with DM1, tend to increase with time, which is a direct sign of ganglion cell damage (Figure 4).

In conclusion, this study showed that VEP is a valuable method to detect diabetic preretinopathy in children suffering from DMI. It is known that therapy for diabetic retinopathy is most effective if it is applied as soon as the first signs of diabetic retinopathy arise. VEP is a non-invasive examination method that facilitates detection of early diabetic retinopathy changes, which is of great value in blindness prevention. This study has also shown that the first pathological neurophysiologic changes in patients with DM1 arise between 8 and 10 years after the onset of diabetes. Future studies should be focused on evaluation of the time that elapses between the appearance of the first detectable pathologic electrophysiologic changes and the first ophthalmoscopically detectable retinal changes in patients with DMI.

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PROMJENE VRIJEDNOSTI KRIVULJE VIDNO EVOCIRANIH POTENCIJALA U RANOM OTKRIVANJU PREDIJABETIČNE FORME DIJABETIČNE RETINOPATIJE KOD BOLESNIKA S JUVENILNIM DIJABETES MELITUSOM

S A Ž E T A K

Cilj ove studije je bio ispitati značaj testiranja vidno evociranih potencijala u otkrivanju oštećenja retinalnih ganglijskih stanica u bolesnika s diabetes mellitus tip 1, koja se javljaju prije pojave prvih oftalmoskopskih znakova dijabetičke retinopatije. VEP testiranje se uradilo u 45 bolesnika podjeljenih u tri grupe; 15 djece s netom otkrivenim diabetes mellitusom, 15 djece koji duže boluju od dijabetesa, 15 zdrave djece kao kontrolne grupe. Statistička značajnost je pronađena u vrijednostima visine amplitude ($Z=4,02$, $p<0,001$) I latencije ($Z=-4,66$, $p<0,001$), između djece koja duže vrijeme boluju od dijabetesa i grupe djece s netom otkrivenim dijabetesom. Tijekom trajanja bolesti vrijednosti amplitude su progresivno padale za vrijednosti latencije su progresivno rasle u djece s dijabetes mellitusom. Vrijednosti latencije krivulja vidno evociranih potencijala su rasle tijekom trajanja bolesti što je direktan znak oštećenja ganglijskih stanica koje su se javile prije prvih oftalmoskopskih znakova dijabetičke retinopatije. Zbog toga je testiranje vidno evociranim potencijalima značajna metoda za otkrivanje prvih znakova retinopatije u djece s dijabetesom mellitusom tip 1.