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Central nervous system tumour diagnosis in pediatric population – the role of an ophthalmologist and the utility of visual evoked potentials

Diagnostyka guzów ośrodkowego układu nerwowego u dzieci – rola okulisty i użyteczność badania wzrokowych potencjałów wywołanych

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Abstract:

Objective: To determine possible alterations of P100 and P1 amplitudes and latencies in school-aged children with a history of a central nervous system tumour.

Material and methods: The pattern visual evoked potential and flash visual evoked potential testing was performed in 42 school-aged children: 15 patients with a history of the central nervous system tumour (mean age of 13.44 ± 2.41 years and 13.75 ± 2.29 years, respectively) and 27 healthy subjects as a control group (mean age 11.84 ± 1.44 years, and 14.78 ± 4.26 years, respectively).

Results: P100 amplitudes of pattern visual evoked potentials were statistically decreased in the study group as compared to the control group. The only statistically signifcant difference between the study group and the controls was latencies recorded from O1 in 15-minute stimuli. P2 amplitudes of flash visual evoked potentials were decreased and latencies were increased in the study group, however, the differences were not statistically significant.

Conclusions: Visual evoked potential alterations can be a sign of functional disturbances of the visual system in patients with any central nervous system tumour. Therefore, a diagnostic process of a central nervous system tumour should include a thorough ocular exam, even in patients with normal visual acuity.

Key words: central nervous system tumours, children, visual evoked potentials.

Abstrakt:

Cel: wykazanie różnic w wartościach amplitud i latencji fal P100 oraz P1 u dzieci w wieku szkolnym, u których zdiagnozowano guza ośrodkowego układu nerwowego.

Materiał i metody: badaniom wzrokowych potencjałów wywołanych stymulowanych wzorcem czarno-białej szachownicy i błyskowych wzrokowych potencjałów wywołanych poddano 42 dzieci: 15 dzieci, u których zdiagnozowano guza ośrodkowego układu nerwowego (średnia wieku odpowiednio: 13,44 ± 2,41 roku i 13,75 ± 2,29 roku), oraz 27 dzieci z grupy kontrolnej (średnia wieku odpowiednio: 11,84 ± 1,44 roku i 14,78 ± 4,26 roku).

Wyniki: w wynikach badań wzrokowych potencjałów wywołanych stymulowanych wzorcem czarno-białej szachownicy stwierdzono statystycznie istotne różnice między parametrami amplitud fali P100 uzyskanymi u dzieci z grup badanej i kontrolnej, istotne statystycznie różnice w wartości latencji fali P100 natomiast wykazano jedynie w odprowadzeniu O1 w stymulacji wzorcem 15 minut kątowych. W badaniu błyskowych wzrokowych potencjałów wywołanych amplitudy fali P2 były obniżone, a latencje wydłużone, niemniej jednak wyniki nie były istotne statystycznie.

Wnioski: zmiany w badaniach wzrokowych potencjałów wywołanych mogą świadczyć o zdezintegrowanej funkcji drogi wzrokowej w przypadku wszystkich guzów ośrodkowego układu nerwowego. U pacjenta, u którego zdiagnozowano guza ośrodkowego układu nerwowego, należy wykonać badanie okulistyczne, nawet wtedy, kiedy stwierdzono u niego pełną ostrość wzroku.

Słowa kluczowe: guzy ośrodkowego układu nerwowego, dzieci, wzrokowe potencjały wywołane.

Introduction

Tumours of the central nervous system (CNS) can affect every part of the visual pathway (1). Childhood tumours directly affecting the visual pathway are commonly connected with type 1 neurofibromatosis (2, 3). However, CNS tumours located outside the visual system can negatively impact vision by compressing visual system structures as they grow (1, 4). Tumour size and location have the most prognostic value for good vision (1).

The availability of reliable instruments to measure the functional integrity of the visual pathway in a patient with a CNS tumour is essential in paediatric ophthalmology (2, 5–7). Reliable examinations are important both before and after surgery, as they detect tumour progression, relapses or regression (1, 2, 4, 8, 9). The value of subjective methods, such as visual acuity or visual field testing is debated, as they need full cooperation of a patient (6, 10–14). The objective methods such as pattern visual evoked potentials (PVEP) and flash visual evoked potentials (FVEP) can be used in such circumstances (2, 6, 7). Visual evoked potentials (VEP) demonstrate changes in the visual system function by indicating a deviation in amplitudes and latencies of P100 wave (PVEP) or P2 wave (FVEP) (1, 2, 4–8).

We examined a group of school-age children with a history of a CNS tumour. We performed PVEP or FVEP to discover possible tumour-induced functional changes in the visual system. We hypothesised that the presence of a CNS tumour would result in altered VEP responses. When abnormal VEP responses were detected, magnetic resonance imaging (MRI) scans of the brain was performed.

Material and methods

The study was performed at the Department of Paediatric Ophthalmology and Strabismus, Medical University of Bialystok. It was approved by the local Internal Review Board and was in accordance with the Declaration of Helsinki.

15 school-aged children with at least six-month history of the CNS tumour were examined. The findings were compared to the ones of healthy controls. In the PVEP study group, the inclusion criteria were history of the CNS tumour and visual acuity over 20/100, whereas high myopia was the exclusion criterion. In the FVEP study group, the inclusion criterion was a history of the CNS tumour and the exclusion criteria were high myopia, risk of epileptic seizure, and lack of parental consent due to that risk.

19 healthy school-aged children born at term were enrolled in the PVEP and in the FVEP control group. All subjects

No./ Nr	Age (years)/ Wiek (lata)	BCVA		VEP		Tumour location/ Lokalizacja guza	Diagnosis/ Rozpoznanie	Surgery/ Operacja
		RE OP	LE OL	PVEP	FVEP			
1	15	20/200	20/100	-	+	*chiasma opticum*	*Glioma*	yes/ tak
2	11	20/20	20/20	+	+	*lobus temporalis sinister*	*Ganglioglioma*	yes/ tak
3	10	20/20	20/20	+	+	*sulcus lateralis, chiasma opticum*	*Cystis arachnoideae*	no/ nie
4	11	20/20	20/20	+	-	*lobus parietalis dexter*	*UD*	no/ nie
						fossa cranii posterior	*Cystis arachnoideae*	
5	15	20/20	20/20	+	+	*hypophysis*	*Cystis epidermalis*	no/ nie
						fossa cranii posterior	*Cystis arachnoideae*	
6	16	20/20	20/20	+	+	*corpus pineale*	*UD*	no/ nie
7	12	20/20	20/20	+	-	*Nervus opticus dexter*	*Glioma*	no/ nie
						hemispherium cerebri sinister	*Hamartoma*	
8	14	20/25	20/20	+	-	*chiasma opticum*	*Lipoma*	no/ nie
						corpus pineale	*Cystis*	
9	12	20/400	20/20	+	-	*chiasma opticum*	*Glioma*	no/ nie
						thalamus, globus pallidus, putamen, pedunculus cerebri, truncus cerebri	*Hamartomas*	
10	14	20/40	20/25	+	-	*tractus opticus sinister*	*Glioma*	yes/ tak
11	15	20/40	20/40	+	-	*cerebellum*	*Astrocytoma pilocyticum*	yes/ tak
12	15	20/20	20/20	+	-	*hypothalamus, hypophysis*	*UD*	no/ nie
13	17	20/20	20/63	+	-	*fossa cranii posterior*	*Cystis arachnoideae*	no/ nie
14	12	20/20	20/20	+	-	*chiasma opticum*	*Cystis arachnoideae*	no/ nie
15	15	NLP	20/20	+	+	*lobus temporalis sinister*	*Astrocytoma*	yes/ tak

BCVA – the best corrected visual acuity/ najlepsza skorygowana ostrość wzroku, VEP – visual evoked potentials/ wzrokowe potencjały wywołane, FVEP – flash visual evoked potentials/ błyskowe wzrokowe potencjały wywołane, PVEP – pattern visual evoked potentials/ stymulowane wzorcem czarno-białej szachownicy wzrokowe potencjały wywołane, RE – right eye/ OP – oko prawe, LE – left eye/ oko lewe – OL, UD – undefined/ nieokreślony, NLP – no light perception/ brak poczucia światła

Tab. I. The characteristics of the patients in the study group.
Tab. I. Charakterystyka pacjentów z grupy badanej.

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had a visual acuity of 20/20. Their PVEP and FVEP results were used as the reference by the electrophysiology lab in the past 5 years.

The PVEP and FVEP examinations were performed in a laboratory according to ISCEV standards using the Espion Diagnosis equipment, as described in our previous study (15). All data was processed using STATISTICA Version 10 (StatSoft). The Kolmogorov-Smirnov test (KS-test) and student's t-test were performed. The P100 wave latencies and amplitudes in 15- and 60-minute stimuli as well as P1 wave latencies and amplitudes obtained from the O1, Oz and O2 electrodes were compared between the patients and controls.

Results

A total of 15 school-aged children (10 boys and 5 girls) aged 10–17 years (mean: 14.67 ± 1.63 years) with a history of the CNS tumour were enrolled. Five children (33.3%) had previous neurosurgical procedure, whereas watchful waiting is used in other 10 patients. Five children (patients number 4, 5, 7–9 in Table I) had more than one CNS tumour. In 6 patients, intracranial lesions were located outside, and in 9 patients within or near the visual pathway. Tumour diagnosis was based on histopathologic examination or MRI image. Eight children (53.3%) had bilateral visual acuity of 20/20. None of them presented with signs of intracranial hypertension. PVEP was performed in patients with best corrected visual acuity (BCVA) > 20/100. FVEP was discarded if no parental consent was given. Overall, 27 eyes for PVEP and 12 eyes for FVEP were included in the analyses as the study group. The mean age in the PVEP study group was 13.44 ± 2.41 years, as compared to 13.75 ± 2.29 years in the FVEP study group. The baseline characteristics of the study group are summarized in Table I.

27 school-aged children aged 10–17 years (mean: 12.2 ± 3.18 years) were enrolled in the control group. Overall, 38 and 9 eyes were included in analyses as PVEP and FVEP controls, respectively. The mean age in the PVEP control group was 11.84 ± 1.44 years as compared to 14.78 ± 4.26 years in the FVEP control group. KS-test confirmed normal distribution

VEP electrode/ Elektroda VEP	PVEP Parameters/ Parametry PVEP	Control group (n=38) Mean ± SD/ Grupa kontrolna		Test group (n=27) Mean ± SD/ Grupa badana		Significance of difference/ Poziom istotności p	
		15 min	60 min	15 min	60 min	15 min	60 min
O1	P100 latency (ms)/ Latencja P100	103.14±4.19	101.12±5.44	112.68±14.31	107.49±19.83	P<0.001*	P<0.06
	P100 amplitude (μm)/ Amplituda P100	14.51±5.4	14.81±5.01	7.74±4.47	8.72±4.29	P<0.001*	P<0.001*
Oz	P100 latency (ms)/ Latencja P100	104.14±3.6	100.03±3.88	107.1±24.46	104.49±17.54	P<0.48	P<0.13
	P100 amplitude (μm)/ Amplituda P100	23.83±8.85	23.75±8.31	10,71±7.41	11.03±6.51	P<0.001*	P<0.001*
O2	P100 latency (ms)/ Latencja P100	104.93±4.63	101.11±4.64	101.87±22.52	106.86±20.54	P<0.42	P<0.1
	P100 amplitude (μm)/ Amplituda P100	14.72±6.36	14.61±5.6	7.95±7.29	9.83±6.33	P<0.001*	P<0.001*

VEP – visual evoked potentials/ wzrokowe potencjały wywołane, PVEP – pattern visual evoked potentials/ stymulowane wzorcem czarno-białej szachownicy wzrokowe potencjały wywołane, n – number of eyes/ liczba oczu, *difference was significant at the p <0.05 level/ poziom istotności znamienny, gdy p <0.05

Tab. II. PVEP values in the test group and the control group (Student's t-test).
Tab. II. Wyniki PVEP u pacjentów z grup badanej i kontrolnej (test t-Studenta).

VEP Electrode/ Elektroda VEP	FVEP parameters/ Parametry FVEP	Control group (n=16) Mean ± SD/ Grupa kontrolna	Test group (n=9) Mean ± SD/ Grupa badana	Significance of difference/ Poziom istotności p
O1	P2 latency (ms)/ Latencja P2	100.57±9.51	99.88±30.52	P<0.95
	P2 amplitude (μm)/ Amplituda P2	12.15±.6.9	10.11±6.0	P<0.37
Oz	P2 latency (ms)/ Latencja P2	99.4±8.27	105.63±16.36	P<0.3
	P2 amplitude (μm)/ Amplituda P2	14.5±5.99	11.83±6.45	P<0.32
O2	P2 latency (ms)/ Latencja P2	98.7±8.91	101.36±26.69	P<0.32
	P2 amplitude (μm)/ Amplituda P2	13.23±6.71	10.88±5.54	P<0.36

VEP – visual evoked potentials/ wzrokowe potencjały wywołane, FVEP – flash visual evoked potentials/ błyskowe wzrokowe potencjały wywołane, n – number of eyes/ liczba oczu

Tab. III. FVEP values in the test group and the control group (Student's t-test).
Tab. III. Wyniki FVEP u pacjentów z grup badanej i kontrolnej (test t-Studenta).

of the data, whereas the student's t-test revealed no statistically significant age differences between the study and the control group.

The components of PVEP, that is the latencies of P100 wave in a 15- and 60-minute check stimulation, varied in schoolchildren with a history of CNS tumour as compared to their healthy peers (Student's t-test). The P100 latency was delayed in the study group as compared to controls (Tab. II). However, the only statistically significant difference was in responses obtained from O1 electrode in 15-minute check stimuli ($P < 0.001$). The remaining PVEP parameters – the P100 wave amplitudes – were lower in the study group as compared to the control group (Student's t-test) (Tab. II).

The differences in all responses obtained from O1, Oz and O2 electrodes in 15- and 60-minute check stimuli were statistically significant ($P < 0.001$).

The components of FVEP, that is the latencies and amplitudes of P2 wave in a flash stimulation, varied in schoolchildren with a history of the CNS tumour as compared to their healthy peers (Student's t-test). The P2 latency was delayed and amplitudes were lower in the study group as compared to controls. However, the differences were not statistically significant (Tab. III).

Discussion

VEP testing involves recording the response of the occipital cortex to the stimulation of the central visual field (5). Two types of stimuli can be used in eliciting the visual evoked responses: the pattern and the light. PVEP is a simple, sensitive and objective technique for evaluating impulse conduction along the visual pathways. It can detect any defect from optic nerve to occipital cortex. Nevertheless, the choice of the most appropriate stimuli depends on patient visual acuity and their ability to cooperate during the procedure. PVEP is the first choice examination, due to the higher repeatability of obtained values. However, in patients with poor visual acuity (below 20/200) or uncooperative, FVEP needs to be performed to ensure the objective functional assessment of the visual system (2).

The VEP analysis differs between children and adults (16, 17). In children, latencies and amplitudes are higher as compared to adults. However, electrophysiological activity matures, so the latencies and amplitudes of P100 wave decrease with time over childhood (17). Changing PVEP results reflect the structural development of the CNS (18, 19).

Paediatric ophthalmology greatly benefits from the objective methods of visual system assessment (2, 5–7). Although in children with normal visual acuity, reliable outcomes are assumed to be achieved with a standard ocular examination, the study by Kelly et al. showed that the sensitivity of visual acuity testing is lower as compared to VEP in the detection of early optic nerve damage in children (6, 10–14, 15, 20). Nearly one-fourth of children in their study presented with normal visual acuity when diagnosed with optic pathway glioma, whereas VEP was abnormal in each of these patients (20). Therefore, in patients with known CNS tumour history, the opportunity to objectively assess visual system function with VEP is valuable (1, 6–9).

Ophthalmologist, neurologists and neurosurgeons have some diagnostic armamentarium at their disposal to detect and monitor CNS tumour progression with the most precise structural assessment possible using the MRI (21). However, even the best structural assessment cannot replace the functional diagnosis of the visual system (2). VEP is used for assessing the functional integrity of the visual pathway and excels over any known scanning technique.

Our study confirmed differences in PVEP and FVEP responses between children with history of the CNS tumour and their healthy peers. The statistically significant differences in P100 amplitudes seem to support that the CNS tumours located not only within but even outside the visual pathway alter the visual evoked responses. The statistically significant differences between the study group and controls in P100 latencies recorded from O1 electrode in 15-minute pattern stimuli are suggestive of sectorial disturbance visual stimulus conduction in patients with CNS tumours. However, the absence of statistically significant differences in P100 latencies recorded from other electrodes can reflect possible good visual acuity in children with the CNS tumours located outside the visual system.

According to Wenzel et al., the PVEP is an excellent tool in a long term follow-up of patients with large cancerous lesions along the visual pathway due to its high sensitivity and a full safety (22). PVEP is even more sensitive than visual acuity testing in cooperative patients (22). Lorenz et al. concluded that VEP alterations can be observed in patients with any brain tumour (1). Obviously, the significance of alterations in VEP responses mainly depends on the CNS tumour location. However, tumour grading and size can also induce changes in the VEP responses. Lorenz et al. suggested that children with any brain tumour should be examined by the ophthalmologist not only during diagnostic assessment, but also before and after any neurosurgery, radiotherapy or chemotherapy. Christophis et al. highlighted the fact that VEP alterations in patients with previous brain tumour can be caused not only by tumour compressing the optic pathway, but also by hydrocephalus (4). In their study of posterior fossa tumours, over half of patients with abnormal VEP were shown to have hydrocephalus and the reported VEP alterations involved mainly an increase of the cortical potential latency.

Additionally, VEP changes should be monitored not only in relapse, but also during recovery after the brain tumour surgery (8). Pojda-Wilczek et al. confirmed that resection of pituitary tumours compressing the visual tract could improve VEP results (8). In their research, the P100 amplitudes were increased and latencies shortened after surgery. Also in the study by Kelly et al., the VEP confirmed stabilisation of visual pathway function with treatment (20).

Still, we acknowledge that our study has some limitations. First, the number of patients in the study groups was low. Second, obtaining reliable and statistically significant results was impossible due to the low number of patients in the FVEP control group. Enrolling more patients in the FVEP control group would likely ensure an improved p-value. However, children with good visual acuity are rarely seen by ophthalmologists and the increased risk of epileptic seizures associated with flash stimulation prevents some parents from consenting to have their children examined with FVEP rather than PVEP.

Conclusion

VEP alterations can signify functional disturbances of the visual system in patients with any CNS tumour. Therefore, a dia-

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gnostic process of a CNS tumour should include a thorough ocular exam, even in patients with full visual acuity.

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