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THE ROLE OF THE VISUAL EVOKED POTENTIALS IN DIAGNOSING AND MONITORING PITUITARY ADENOMAS

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ABSTRACT:
THE VISUAL EVOKED POTENTIALS (VEP) IS A NON-INVASIVE AND REPETITIVE TEST THAT CAN EVALUATE THE EVOLUTION OF A DISORDER OF THE OPTIC PATH. THE AIM OF THIS STUDY WAS TO EVALUATE THE DIAGNOSTIC VALUE OF VEP IN THE EXPLORATION OF THE OPTIC CHIASM SYNDROME IN THE COMPRESSIVE SELLAR CONDITIONS. WE PERFORMED THE ELECTROPHYSIOLOGIC EXAMINATION (VEP) AND OPHTHALMOLOGIC EXAMINATION (VISUAL ACUITY, VISUAL FIELD, FO OPTIC FUNDUS) IN A GROUP OF 51 PITUITARY ADENOMAS PATIENTS AND A 90 HEALTHY SUBJECTS CONTROL GROUP, OF A TOTAL OF 114 STUDIED PITUITARY ADENOMAS. WE NOTED AN INCREASE IN THE LATENCY OF THE P100 WAVE THAT STATISTICALLY CORRELATES WITH THE VISUAL FIELD MODIFICATION. THE ADENOMA INDUCED CHANGES WERE BETTER EXPRESSED IN THE HALF FIELD STIMULATIONS (THF, NHF) – WE RECORDED A SIGNIFICANT GREATER INVOLVEMENT IN THE TEMPORAL FIELD COMPARED TO THE NASAL FIELD.VEP HAVE A GREATER DIAGNOSTIC VALUE COMPARE TO THAT OF THE VISUAL FIELD IN REVEALING THE OPTIC CHIASM COMPRESSION (76.5% VS. 68.6%). THEY CONFIRM THE VISUAL DEFICIT SHOWED BY THE PERIMETRY AND PERFECTLY REVEAL THE OPTIC PATHS' INVOLVEMENT. IN CONCLUSION VEP IS AN INVESTIGATION OF GREAT VALUE IN EVALUATING THE PITUITARY ADENOMA REVEALING FUNCTIONAL ALTERATIONS PRIOR TO THE CLINICAL FEATURES.

KEYWORDS: PITUITARY ADENOMAS, VISUAL EVOKED POTENTIALS, P100 WAVE, HALF FIELD STIMULATIONS

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INTRODUCTION

The visual evoked potentials (VEP) represent electric manifestations in the reception of external stimuli and the responses generated by these stimuli, registered within some components of the nervous system. The responses evoked through the sensitive-sensorial of the peripheral receptors evidence the activity of one or more neural complexes, reflecting the aspect of the mechanisms involved in processing the specific sensorial information[10],

Concerning the VEP, it was achieved the recording of the bioelectrical activity of the retina, the optic nerve, lateral geniculate nuclei, optic radiations, visual cortex, being evidenced many types of neurons that respond differently to the light stimulation. VEP findings contributed to understanding whether the dysfunction originated was at the retina, in the optic nerve, chiasm or postchiasmal pathway[11].

EP (evoked potentials) have attained a wider applicability, the method imposing itself firmly in various fields[12]. Thus, EP are used in: the positive and differential diagnose of the central and peripheral nervous system diseases (demyelinating diseases, medullar/intracranial tumors, traumatic lesions, inflammatory lesions, spinal and intra-skull neuropathies), they contribute to the evaluation and prognosis of the mental functions in congenital and degenerative conditions (through the evaluation of the auditory function, the estimation of visual acuity, the intra-operatory monitoring, the monitoring in the intensive care services – post-operatively, in coma cases)[13].

In the present work, the VEP are studied within the diagnosis and the post-operation evolution of the pituitary adenomas.

VEP can be induced through unstructured light stimuli (flash) or structured light stimuli (pattern).

Nowadays, it is preferred the designation of the maximal points through a combination of letters and numbers, N representing “negativity”, and P “positivity”; the numbers indicate, in milliseconds, either the average value of the normal latency for the peak or the value of the calculated latency for a specific studied case (real value)[14].

The visual stimulation is done with the help of a controlled light source. The light source can be used in two different ways: as a visual stimulus that produces a change of the luminance (light exposure for a determined time, then darkness), realizing a flash-type stimulation and as a visual stimulus obtained by changing the image, while the quantity of light remains unchanged, realizing a “pattern” or “pattern-reversal” type stimulation.

A normal visual evoked potential has the following elements:

a) A primary complex, within the 0-100ms interval, interpreted as a local, specific response, probably determined by the pre-synaptic activity from the thalamo-cortical afferents that originate in layer IV of the visual cortex.

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[13] Lachowicz,Ewelina; Lubinski, Wojciech; *The importance of the electrophysiological tests in the early diagnosis of ganglion cells and/or optic nerve dysfunction coexisting with pituitary adenoma: an overview* - Doc Ophthalmol, 137:193–202, 2018;

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b) A secondary complex, between 100 and 200ms – a more generalized cortical response, whose major component would be determined by the multi-synaptic activity from the intra-cortical neurons.

c) A rhythmic post-discharge, within the 250-1250 ms interval, interpreted as a "rebound" phenomenon of the cortical rhythmic activity, that was blocked by the stimulus.

Generally, the greatest amplitude of the VEP is registered on the median line, next to the inion, yet not all the waves register their maximal values in this area. In practice, the positive P_{100} wave, which appears at 100ms after the stimuli, is the most frequently analyzed, while being the most constant and easy to identify wave.

The purpose of this work is to specify the onset, evolution and post-therapeutic particularities of a lesser used method, the visual evoked potentials, in the diagnosis of the pituitary adenomas. They allow the assessment of the degree of suprasellar extension of these tumors, thus leading to a new approach of the pituitary tumors' management.

The study intends the comparative evaluation of the electro-physiological exploration (VEP) of the patients with operated or non-operated adenomas *versus* control subjects.

MATERIAL AND METHOD

The study was carried out retrospectively within the Emergency Clinical County Hospital of Craiova, analyzing the medical records over a 10-year period of time (2006-2016).

The presented study group consisted of 114 people suffering from pituitary adenomas and 14 people suffering from *empty sella* syndrome, hospitalized in the Endocrinology Clinic and later monitored. It is worth mentioning that the empty sella syndrome was an imagistic diagnosis stage of the people suffering from sellar radiological alterations, who also displayed, or not, the endocrine features. The control group consisted of 91 healthy subjects, equally distributed pertaining age and sex as the patients in the adenomas group.

The electro-physiological exploration was performed in the Electro-Physiology Laboratory of the Emergency Clinical County Hospital of Craiova, in order to assess the visual evoked potentials. From the multitude of possibilities, we chose the mediation method. According to the mathematical argumentation, the signal/noise *ratio* is improved, its value being of Vn (n representing the number of summarized waves). In order to apply the mediation method, the computer, synchronized with the generation of each stimulation, takes 500 samples from each patient.

After the computer has all the 500 samples stored, a point by point summarization is performed, resulting in an average of all the waves generated by the stimulation at that moment.

After ending this mediation process, the computer screen displays the shape of the wave. Certain parameters are measured: the latency, the duration, the amplitude, the peak-to-peak amplitude, the suddenness, the area. the numbers indicate, in milliseconds, either the average value of the normal latency for the respective peak (the theoretical value), or the value of the latency calculated for a certain studied case (the real value).

For making these determinations, the examiner has to mark, for each wave from the macular complex (N_{75}, P_{100}, N_{135}), the beginning, the peak and the end. The calculations do not condition the marking of all these elements, being known the fact that there are sufficient situations in which not all these channels can be evidenced.

The operator obtains these results either as a graph, in which the values are presented, or as a report. For the collection of the bio-potentials, several electrodes were used.

The stimulation was made with a LED *full field* reversal pattern, the alternative change of the bars being made to every 1-1.5 seconds, and, in selected cases, the stimulation with *half field*.

It is worth mentioning that, before the testing, the patients' refraction deficits were corrected. During the test the patients were instructed to find a fixed light point of a different color situated within the centre of the stimulation area and focus on it. Then200-250 responses were gathered and mediated, with a frequency of 1000/s, and a digital-analogous resolution of 12 bits.

Methods of statistical processing of the data

For the processing of data, there were used the software packs **Microsoft Excel**, **EPI2000**, distributed by OMS, **SPSS**, specialized in scientific statistic calculations, produced by SPSS company and the **Statistics**, a program for statistical processing and graphic, produced by Stat Soft.

The registering of the information concerning the patients, with the help of MS Excel program, represented the initial database, from which the significant aspects of this study were extracted.

THE OBTAINED RESULTS

The set of adenomas was represented by 114 patients, aged between 15 and 73 years old, with an average of 44.73 years old, with a 15.06 SD,

Subset A consisted of 77 patients with pituitary adenomas, for which there was not practiced the curative surgical intervention, aged between 15 and 73 years old, with an average of 44.61 years old.

Subset B was composed of 37 patients with pituitary adenomas, to which there was practiced the trans frontal and transsphenoidal pituitary resection, aged between 15 and 66 years old, with an average of 45.62 years old.

Subset C consisted of 14 *empty sella* patients, aged 31 to 67 years old, with an average of 50.86 years old. Subset D had 91 healthy subjects.

The entire group of adenoma patients and the subsets of people with operated and non-operated adenomas, along with the subset of *empty sella* patients were analyzed according to age group.

The gender distribution of the subsets revealed a clear preponderance of the females against the males. Thus, we recorded a frequency of adenomas in women of 64% (73 cases), compared to 36% in men (41 cases), with a 1.77 / 1 sex *ratio* (F/M). Minderman and Wilson communicated a similar women/men *ratio* (2/1), a *ratio* with a higher value, probably due to the higher share of the prolactinomas in the study sets, the most frequent pituitary tumor in women[15].

In practice, the P_{100} positive wave that appears 100ms after the stimuli, is the most frequently analyzed, being the most constant and easy to identify wave. The relative amplitude of this wave presents inter-individual variations, between 5 and 15 μV, but the general morphology and, especially, the latency of the P_{100} wave is sufficiently stable.

The aspect of a normal VEP–(figure 1) On the obtained records, there were analyzed the waves of the $N_{75}P_{100}N_{135}$ macular complex, where they were present, P_{100} wave remarking as a reliable marker.

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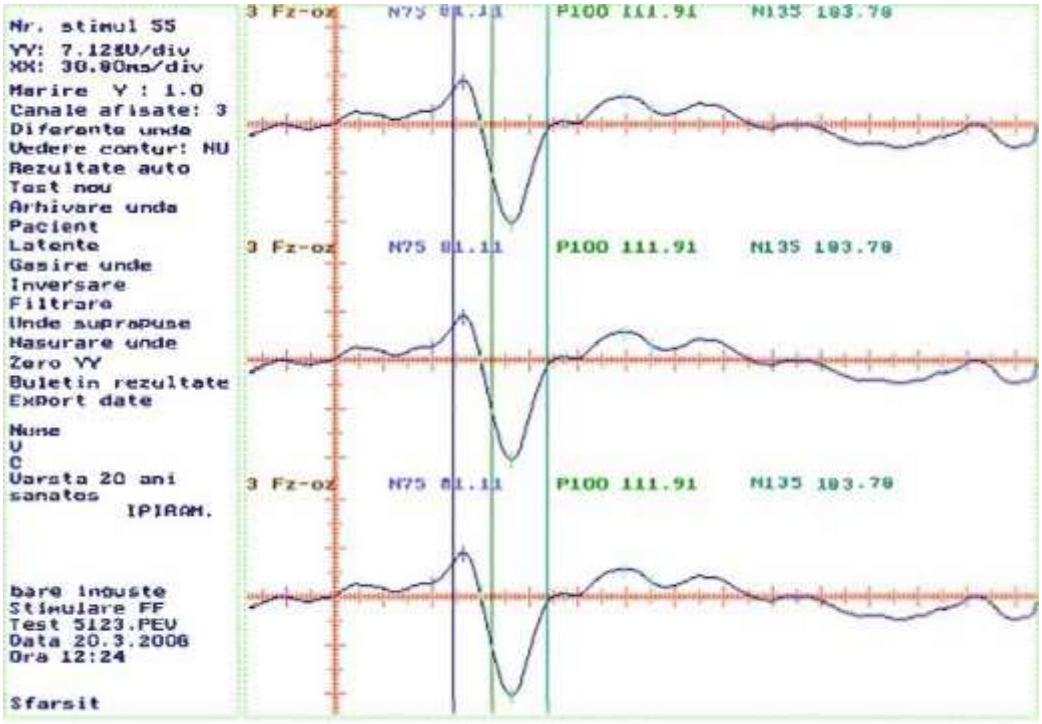
On this wave, it was evaluated:

- from the moment of the stimulation to the shaping of the peak – the normal values latency, in the conditions of the Electrophysiology Laboratory, of up to 115ms (with an average of 106ms).

- interocular differences of the latency (between OD and OS on the same derivation) with normal values of up to 7ms.

- P_{100}wave amplitude.



(figure 1) - The aspect of a normal VEP

Briefly,VEP reflects well the deficit registered at perimetry. Optic nerve changes are observed, even if the other tests of exploration are still normal; this increased sensitivity is counterbalanced by the difficulties in more subtle interpretation, than in perimetry.

In the studied patients, we obtained the following statistical indicators for the evoked potentials latencies.

Comparisons between adenoma and control

We calculated the latencies of the main waves of the $N_{75}P_{100}N_{135}$ macular complex in the study group compared to the control group using Anova test.

N_{75}Wave. For the N_{75} wave, the wave latency was of 81.54ms for the adenoma set and 77ms for the control group, the difference being statistically significant ($p<0,016513$).

The minimal and maximal values of the N_{75} wave latency for the adenoma set were 54 and 126 ms and 56.98 and 102.1ms for the control group (table 1).

(table 1)

The statistic indicators of the N_{75} wave latency

	Minimal	Q1 Quartile	Median	Q3 Quartile	Maximal
Adenoma	54.76	74.44	80.09	87.61	126.28
Control	56.98	71.615	77.105	81.45	102.1

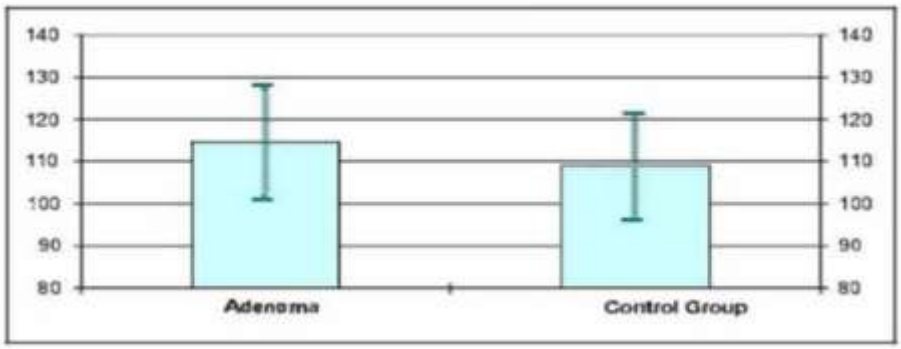
P_{100} Wave

The average of the P_{100} wave latency was 114.53ms for the adenoma set, compared to 108.8ms for the control group, the difference being statistically different (table 2, fig 2).

(table 2)

P_{100} wave latency

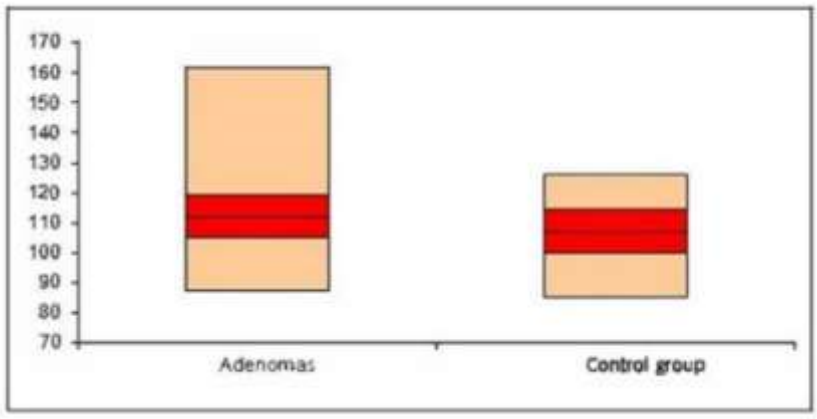
L100	No. of patients	Average	Standard deviation	p-statistical
Adenoma	51	114.53	13.706	0.013389
Control	91	108.854	12.651	ANOVA



(figure 2) – The average of the P_{100} wave latency comparison between adenomas and control

The minimal and maximal values of the P_{100} wave latency ranged between 87.27 and 161ms for the adenoma group and between 75.36 and 126.19msfor the control group.

The graph expression of these values with the median and the quartiles is presented in (figure 3).



(figure 3) – The medians, the quartiles, the minimal and the maximal of the P_{100} wave latency.

N_{135} wave

The averages of the N_{135} wave latencies were 156.33 and 155.95ms for the adenoma batch and the control group, respectively, the difference between them being statistically significant.

Comparisons between groups – operated/non-operated/ *empty sella*/adenomas

N_{75} wave. For the N_{75} wave, the average of the latency was of 81.89 ms for the operated adenomas and 81.567ms for the non-operated adenomas. For the *empty sella* cases, the latency average was 80.4ms, and for the control, 77ms, the difference being insignificant.

P_{100} wave. For the P_{100} wave, the latency average was 115.96ms for the operated adenomas, 114.63ms for the non-operated adenomas, 109.86ms for the *empty sella* cases, and 108.8ms for the control, the difference being statistically significant (p-0.04).

N_{135} wave. For the N_{135} wave, the latency average was 155.16ms for the operated adenomas, 158.85ms for the non-operated adenomas, 143.84ms for the *empty sella* cases 155.95msand for the control. The difference is statistically insignificant.

We made a correlation between the VEP signal latency and the size of the tumors – microadenomas (T<10mm) and macroadenomas (T>10mm), but the differences were insignificant (table 3). This might be explained by the fact that, many times, a macro-adenoma of small dimensions does not determine the *optic chiasm* compression.

(table 3)

The statistic indicators of the P_{100}Wave latency for micro- and macro-adenomas

L100	Minimum	Q1 Quartile	Median	Q3 Quartile	Maximal
T<10	96.17	103.96	114.13	120.33	161.88
T>10	87.27	106.93	111.695	117.98	144.15

On the other hand, we met VEP modifying micro-adenomas (2 patients of 19 with microadenomas – 10.5%).

Considering the fact that between the pituitary gland and the optic chiasm there is a distance of approximately 8-10mm, we made correlations between the dimension of the tumor (less or more than 20mm) and the VEP modifications (table 4)

(table 4)

Correlations between the wave latencies modifications and the size of the tumor

Wave		T<20mm	T>20mm	p
N_{75}	No. of patients	41	9	
	Latency average	83.71	74.63	
	Standard deviation	11.33	9.70	0.0308
P_{100}	No. of patients	42	9	
	Latency average	116.35	106.04	
	Standard deviation	13.70	10.69	0.0394
N_{135}	No. of patients	34	6	
	Latency average	157.11	151.92	
	Standard deviation	16.83	20.41	0.5032

The average of the N_{75} and P_{100} wave latencies were 83.71 and, respectively, 116.35ms, in case of tumors with a diameter smaller than 20mm and of 74.63, respectively 106.04ms, in case of tumors bigger than 20mm, the differences being statistically significant ($p<0.03$ in both situations).

We established correlations between the VEP latencies and the modifications of the visual acuity and the visual field. We present below only the situations in which the differences were statistically significant. Concerning the N_{75} wave, the modification of the latencies was statistically correlated both to the visual acuity alteration (table 5) and those from the visual field - table 6 ($p<0.03$*vs.* $p<0.01$). Also, the modifications of the P_{100} wave latencies correlated only to the modification of the visual field ($p<0.03$).

(table 5)

Correlations between the N_{75} wave latency and the modification of the visual acuity

L75	**All**			
Visual acuity	**No. of patients**	**Average**	**Standard deviation**	**p**
Changed	22	84.386	11.226	0.032328
normal	28	77.547	12.31	

(table 6)

Correlations between the N_{75} wave latency and the modification of the visual field

L75	**Only for non-operated**			
Visual field	**No. of patients**	**Average**	**Standard deviation**	**p**
Changed	13	85.972	13.112	0.018159
normal	18	74.831	9.066	

(table 7)

Correlations between the P_{100} wave latency and the modification of the visual field

L100	**Only for non-operated**			
Visual field	**No. of patients**	**Average**	**Standard deviation**	**p**
Changed	13	118.673	14.365	0.037373
normal	18	108.915	14.322	

The duration of the waves did not register modifications; therefore, we only present the minimal, statistically insignificant variations of the P_{100} wave-table 8.

(table 8)

P_{100}wave duration on groups

P100 duration	**Minimal**	**Q1 Quartile**	**Median**	**Q3 Quartile**	**Maximal**
Non-operated	25.15	37.64	43.51	52.02	65.54
Operated	29.94	34.05	35.42	42.09	62.89
Healthy	16.43	37.65	44.56	51.85	89.32

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In conclusion, the P_{100} wave was noticed as a reliable marker, and less the N_{75} wave, for significant increases of the latencies.

From the total number of the analyzed patients, VEP were modified in 73.9%, compared to 79% described in the literature. We noticed 7 patients with normal visual field, but with modified VEP, and also 2 patients with modified visual field (with insignificant deficits) and normal VEP. Considering that, within the optic chiasma syndrome exploration, the testing of the visual field is the first intention, we evaluated the comparative diagnostic value of the two explorations and noted that the VEP objectify better the sufferance of the optic channel compared to the visual field testing-table 9.

(table 9)

The diagnosed value of VEP

Results	**Normal**		**Pathologic**	
Exam	No of patients	%	No of patients	%
Campimetry	14	30.4	32	69.6
PEV	12	26.08	34	73.92

In some of the tested patients we performed a *half-field* stimulation, in order to observe the alteration of the optic nerve fibers of chiasma.

Anatomically, the fibers from the nasal retinal area are crossing within the optic chiasm, and those from the retinal temporal area move on a straight direction towards the relay stations. The name of nasal or temporal area does not reflect the stimulated retinal area, the retinal portion being the opposite of the stimulated field itself.

(table 10)

The latencies of the P_{100} wave, comparison between nasal and temporal stimulation

	No. of patients	**Average of latency**	**Standard deviation**	**p**
NLLS100	26	107.843	15.763	0.00676
TLLS100	26	119.136	13.137	
NLLD100	27	11.085	11.859	0.006159
TLLD100	27	118.375	18.546	

In the half-field stimulations, there were recorded significant differences between the temporal and nasal stimulation, for the both eyes-table 10.

Through this processing we noted the usual modification of the obtained parameters through the stimulation with THF (temporal half-field), which generate the stimulation of the retinal nasal area, these fibers being tightly connected with the sellar comprehensive processes. Sometimes, monocular crossed asymmetries and intraocular differences of the latency can be observed.

DISCUSSIONS

The visual evoked potentials represent an electrophysiological exploration that brings information on the quality of the neural message transmitted through the optic channels

towards the cortex[16]. Although the modifications of the waves are not specific to a certain disease, in clinical context and corroborated with other explorations, the VEP evidence the degree of functional alteration of the retinal-cortical ensemble[17]. It is a repetitive non-invasive exploration that can evidence the evolution of an optical channel alteration[18].

The registering through an occipital electrodes crown, through the monocular stimulation on each half-field, evidences the existence of a chiasmatic alteration. The compression produced by the tumor has repercussions on the transmission of nervous impulse detected through the VEP recording[19]. Two constants are systematically searched for: the period of latency (expressed in milliseconds - ms) and the amplitude of the waves (expressed in microvolts -μV).

In the present study we observed:

- the increase in the latency time of P_{100}wave;
- the decrease of the amplitude of P_{100}wave, a slightly modified parameter;
- monocular crossed asymmetry; interocular latency differences;
- waves'morphology modifications, especially post-surgery.

Of all these modifications, only the increase in the P_{100} wave latency was statistically significant.

For the analyzed patients, we noted an increase in the latency time of the P_{100} wave (most constantly evidenced), which proves the compressive aspect of the adenoma and the diminishing of nervous speed transfer. This modification was correlated statistically with the modification of the visual field (VF) ($p<0.03$).

The VEP amplitudes were reduced in the areas with visual field defect[20].

The changes produced by adenomas were better evidenced in half-field stimulations (THF, NHF), where we observed a greater alteration of the THF than the NHF, statistically significant.

The amplitude of the waves was less influenced, probably due to some technical factors, related to the monopolar character of the recording. Different authors remark a decrease on the wave amplitude, which represents, equally, a direct involvement of the nervous fibers[21].

From the analyzed aspects within the VEP, we observed a higher diagnostic value than that of the visual field in evidencing the chiasmatic comprehension (73.92% confronted to 69.6% of the VF).

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The higher latencies within the subset of operated adenomas, compared to the non-operated patients and the controls, the explanation being related to the increase frequency of the macroadenomas from this subset.

If we consider the Hardy classification into micro- and macro-adenomas, the dimension of 10mm of the tumor did not correlate significantly with the VEP modifications. Yet, considering the distance between the pituitary gland and the optic chiasmis approximately 8mm, we tried to establish a correlation between the 20mm dimension of the tumor and VEP, which was statistically significant ($p<0.03$).

When comparing our results to the relevant aspects from the literature, there were noticed similar parameters with the ones quoted by most of the authors[22].

VEP is accurately framed within the wide range of investigations of the sellar compressive processes, having the advantage of evidencing the functional modifications that can occur even before the clinical ones[23]. The objective changes of VEP may appear earlier than the defect of visual field[24].

CONCLUSIONS

1**.** The visual evoked potentials are a supplemental method in the range of paraclinical investigations for an early positive diagnosis of the pituitary adenomas.

2. Analyzing the waves of the macular complex of the VEP, there were observed waves' latency and morphology alterations, especially of the P_{100} wave and less of the N_{75}wave.

3. The diagnosis algorithm in the pituitary adenomas is significantly improved through the association with some modern paraclinical investigations.Thus, the routine electrophysical exploration ought to be introduced in evidencing the sellar compressive processes.

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