



Preoperative visual evoked potential in the prediction of visual outcome after pituitary macroadenomas surgery

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Abstract

Objective The purpose of the present study is to investigate longitudinal changes in Visual evoked potential (VEP) parameters as an objective test after transsphenoidal surgery, its correlation with subjective tests and clinical value of VEP in the prediction of visual outcome.

Methods Fifty patients with pituitary macroadenoma who underwent surgical removal of the tumor recruited in this study. All the patients underwent ophthalmic examination, static automated perimetry (SAP), VEP and magnetic resonance imaging (MRI) preoperatively and 3 months after surgery.

Results Fifty patients with pituitary macroadenoma (size: 25.1 ± 9.9 mm) were recruited in the study. Before surgery, the pattern of VEP showed a prolonged latency with reduced amplitude in eyes with abnormal visual acuity or abnormal visual field. The P100 wave latencies and amplitudes showed significant correlation with visual acuity and SAP scores. After surgery, visual acuity and visual field improvements were seen in 51% and 65.6% of eyes, respectively. Mean SAP and visual acuity scores increased significantly ($p < 0.01$), P100 wave latency declined and amplitude improved after surgery but not significantly. The mean age of patients, size of tumors and preoperative P100 wave latency were significantly lower in eyes with visual field and acuity improvement.

Conclusion VEP is a helpful quantitative and objective complementary test to visual acuity and SAP exams for assessing pre-operative visual abnormalities and post-operative visual outcome in patients with pituitary macroadenoma.

Keywords Pituitary adenoma · Standard automated perimetry · Transsphenoidal surgery · Visual acuity · Visual evoked potential · Visual field

Introduction

Pituitary adenomas account for 15% of all intracranial neoplasms [1]. The majority of patients present with visual symptoms including visual acuity decline, visual field defect and ocular muscle paresis. Because of anatomical proximity of hypophysis to the optic apparatus, extra-sellar tumor growth particularly in macroadenomas can often lead to optic chiasma compression and visual disturbances. Slowly progressive bilateral and asymmetric visual field defects and optic disc atrophy are typical ophthalmologic changes in these patients [2]. Gradual blindness occurs due to optic nerve atrophy and can be irreversible despite an appropriate treatment [3]. Resolution of compression, ion channel redistribution, remyelination and neural plasticity have been suggested to be involved in the recovery of visual disturbances after the surgery [4, 5].

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The extend of visual field defect is usually evaluated by a subjective method such as static automated perimetry (SAP) which is a clinical gold standard for documenting loss of visual sensitivity. Visual evoked potentials (VEP) objectively assess the function of optic nerve and chiasm and eliminate the factor of subjectivity and patient cooperation needed for SAP [6]. Visual evoked potentials are a complex series of electrocortical fluctuations recorded from occipital scalp during visual stimulation [7]. Compressive lesions around optic nerve may prolong the latency as well as reducing the amplitude of responses [8, 9]. In pituitary adenomas, VEP has been used to discover primary visual disturbances and objectively evaluate progression of visual deficits before surgery and improvement of vision during follow up [10, 11]. Several studies have demonstrated strong correlation between SAP and VEP measures in patients with optic neuritis or multiple sclerosis [12–14].

Because of the critical role of visual system in determining the quality of life, it is necessary to find an objective method to predict visual improvement after surgery. The purpose of the present study is to investigate longitudinal changes in VEP latency and amplitude after transsphenoidal surgery, its correlation with visual acuity and field, and clinical value of VEP in the prediction of visual outcome.

Materials and methods

This study was approved by Tehran University of Medical Sciences Review Board; and written informed consent was obtained from all participants. Fifty patients with pituitary macroadenomas who underwent surgical removal of the tumor in the department of neurosurgery, Imam Khomeini Hospital in 2 years were recruited. All the patients underwent ophthalmic examination, VEP and magnetic resonance imaging (MRI) preoperatively. Exclusion criteria included apoplexy, bilateral visual acuity less than 0.10 and other ocular disease and systemic illness that can affect the retina and optic nerve.

The diagnosis of pituitary adenomas was confirmed by histologic examination. Patients underwent either microscopic or endoscopic transsphenoidal surgery by one neurosurgeon. Patients were re-evaluated with the same examinations 3 months after surgery. Complete optic pathway decompression was achieved in all patients based on post-operative MRI.

Eye examination

The eye examination included visual acuity and visual field assessments, pupil examination, dilated fundoscopy, and VEP by experienced ophthalmologist and neurologist.

Visual acuity was recorded using the Snellen chart and visual field charting done using a Humphrey 750 Visual Field Analyzer II (Zeiss-Humphrey Systems, Dublin, CA, USA) with a central 30-2 threshold protocol. The fixation loss, false positive error and false negative error rates were less than 20%. Eye field was divided into four quadrants. The quadrant with more than 50% involvement considered as abnormal quadrant and scored zero and less than 50% involvement scored 1. Severity of field involvement was analyzed using the sum of each quadrant score, range 0–4 (4 as normal eye field).

The Medelec Synergy device (Oxford instruments, UK) was used for the measurement of VEPs and the latencies and amplitude of VEP components (N75, P100 and N145) were assessed. The monitor was placed at 1 m with 100% contrast sensitivity and 5 cycles per degree. Electrodes were less than 2 K Ω with 1 Hz pulse excitation. VEP Electrodes were placed according to the International 10/20 system. Active electrode was placed on Oz point (5 cm above inion), reference electrode was attached to Fpz and ground electrode was kept on earlobe. The signals were saved as N75, P100 and N145. Calibration is 50 ms and 2.5 mv. The VEP signals were recorded in two rounds in order to access recording accuracy.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 for Windows (SPSS Inc, Chicago, IL, USA). The Student's *t* test (Mann–Whitney tests when appropriate) was used to analyze the statistical differences between means in two groups and Paired sample *t* test (Wilcoxon signed rank tests when appropriate) was conducted to compare means of variables before and after surgery. Comparison of qualitative variants was done by Chi square or Fisher exact test. Pearson's correlation was used to examine association between quantitative data. *p* value less than 0.05 was defined as the limit of significance.

Results

Pre-operative evaluation

Fifty patients, 18 (36%) female and 32 (64%) male with average age of 41.8 ± 11.4 years were recruited for the study. The mean size of tumor based on MRI was 25.1 ± 9.9 mm.

In total, 31% of eyes were defined as abnormal on visual acuity test and 32% showed at least one quadrant field defect on SAP. The average preoperative SAP and the mean visual acuity scores were 3.34 ± 1.12 and 8.39 ± 2.98 respectively. Twelve percent of optic nerves had evidence of optic atrophy on fundoscopic examinations. The mean

P100 wave latency and amplitude were 109.66 ± 15.45 ms and 6.66 ± 3.28 μ V respectively. Pre-operative data are summarized in Table 1.

P100 latencies were significantly higher in eyes with abnormal visual acuity or abnormal visual field. Also, P100 wave amplitudes were significantly lower in abnormal eyes. Therefore, the VEP pattern showed a prolonged latency with reduced amplitude in affected eyes (Table 2). Association between VEP parameters, visual acuity scores, and SAP scores were assessed quantitatively using Pearson's correlation analysis. P100 wave latencies and amplitudes showed significant correlation with visual acuity and SAP scores. (p values < 0.05).

Table 1 Pre-operative patients and tumor characteristics

Variable	
Sex	
Female	18 (36%)
Male	32 (64%)
Age	41.82 ± 11.41 (range 20–64)
Tumor size	25.12 ± 9.96 mm (range 10–60)
Tumor type	
Functional	24 (48%)
Non functional	26 (52%)
Number of previous surgery	
0	47 (94%)
1	1 (2%)
2	2 (4%)
Optic atrophy	12 (12%)
Visual acuity	
Normal	69 (69%)
Abnormal	31 (31%)
Visual acuity score	8.39 ± 2.98
Visual field (SAP)	
Normal	68 (68%)
Abnormal	32 (32%)
SAP score	3.34 ± 1.12
P100 wave latency	109.66 ± 15.45 ms
P100 wave amplitude	6.66 ± 3.28 μ V

Table 2 Pre-operative VEP pattern of normal and abnormal eyes

Pre-operative VEP	Normal VA	Abnormal VA	p value
P100 latency (ms)	105.76 ± 10.62	118.19 ± 20.46	< 0.01
P100 amplitude (μ V)	7.23 ± 3.52	5.42 ± 2.29	0.015
Pre-operative VEP	Normal VF	Abnormal VF	p value
P100 latency (ms)	104.71 ± 8.53	120.52 ± 20.97	< 0.01
P100 amplitude (μ V)	7.56 ± 3.53	4.89 ± 1.69	< 0.01

Post-operative evaluation

All patients underwent transnasal transsphenoidal surgical tumor resection. Microscopic transsphenoidal approach was performed in 7 (14%) patients and endoscopic approach in 43 (86%). The patients were reevaluated at month 3 after surgery.

In 31 eyes with abnormal visual acuity the mean score improved significantly from 4.81 ± 3.19 before surgery to 6.55 ± 3.50 at postoperative month 3 ($p < 0.01$). In these eyes P100 wave latency decreased and amplitude increased post operatively, but these differences were not statistically significant. Overall, visual improvement was observed in 18 (51%) of 31 eyes with preoperative visual acuity impairment. Among 32 eyes showed visual field defects, 21 (65.6%) experienced visual field improvement. The SAP score increased significantly from 1.94 ± 1.01 to 2.97 ± 1.18 postoperatively ($p < 0.01$). P100 wave latency declined and amplitude improved after surgery although not significantly (Table 3). Overall, both conventional tests and VEP values improved due to tumor removal, which led to optic nerves decompression (Fig. 1).

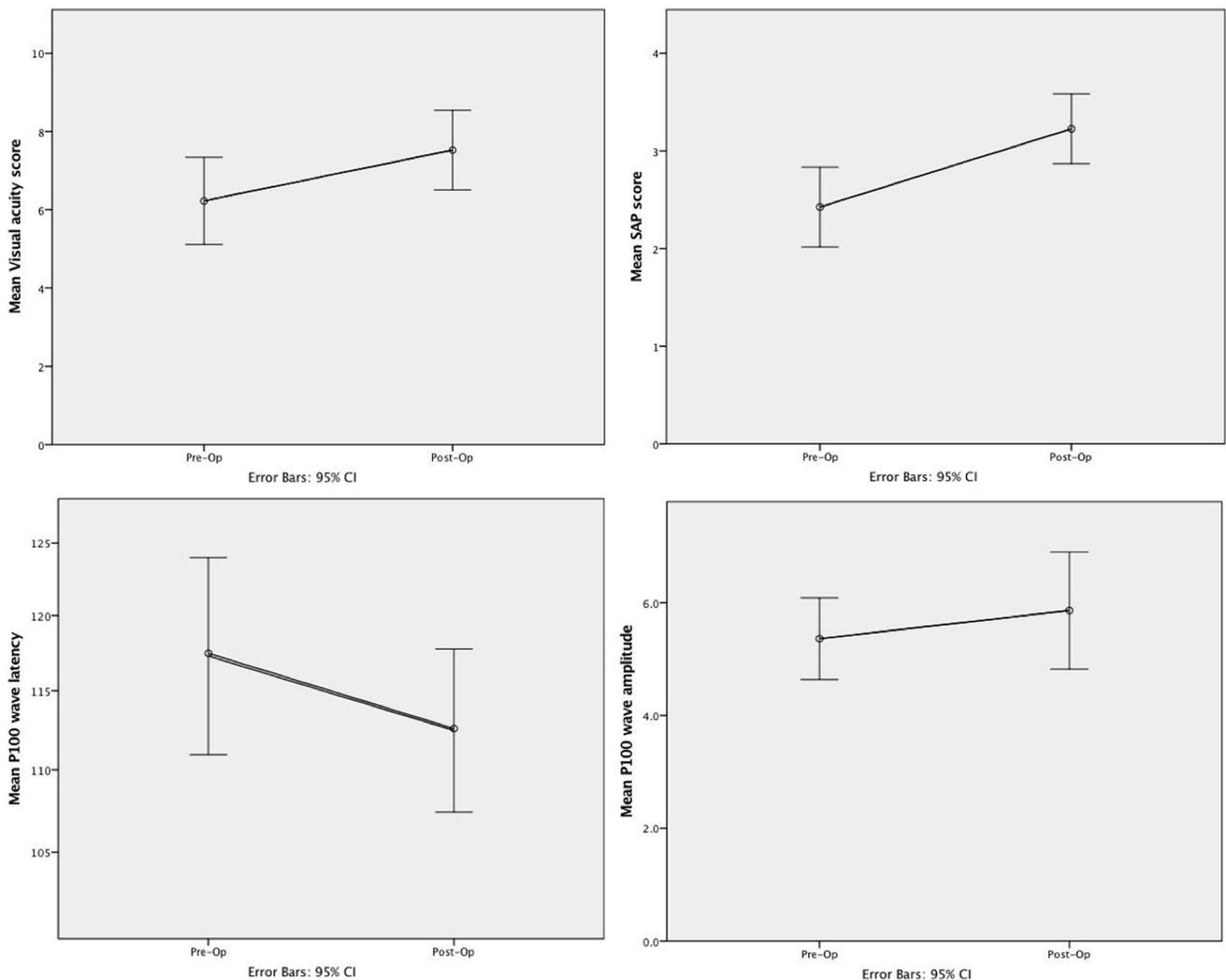
Predictive factors of visual outcome

Statistical analyses were performed to assess the factors affecting the visual outcome (Table 4). Gender, functional status, number of previous surgeries, pre-operative P100 wave amplitudes, post-operative P100 latencies and surgical approach were not significant factors affecting visual improvement. The mean age of patients and the size of tumors with visual field and acuity improvement were significantly lower. Patients who showed optic atrophy had worse outcome. Visual acuity and visual field improvements were significantly lower in this group of patients. The average preoperative P100 wave latency was significantly lower in patients showed visual improvement after surgery.

Figure 2 compares the change of VEP parameters in the eyes showed and did not show visual improvement after surgery.

Table 3 Post-operative VEP measures change in affected eyes

Visual acuity abnormal eyes (N = 31)	Pre op	Post op	p value
Visual acuity score	4.81 ± 3.19	6.55 ± 3.50	p < 0.01
P100 wave latency (ms)	117.07 ± 19.34	110.97 ± 15.49	0.127
P100 wave amplitude (μV)	5.72 ± 2.31	6.13 ± 3.02	0.519
Visual field abnormal eyes (N = 32)	Pre op	Post op	p value
SAP score	1.94 ± 1.01	2.97 ± 1.18	p < 0.01
P100 wave latency (ms)	119.55 ± 20.06	114.24 ± 16.68	0.195
P100 wave amplitude (μV)	5.04 ± 1.75	5.82 ± 2.81	0.194

**Fig. 1** Overall change in visual acuity score, SAP score, P100 wave latency and amplitude following surgery in affected eyes

Discussion

Chiasmal compression due to pituitary macroadenomas is a known cause of visual symptoms including visual acuity

loss and visual field defects. Therefore, visual impairment is an important indication of pituitary adenoma surgical resection. In this study we evaluated optic nerve function before and after the resection of pituitary macroadenomas and examined association of VEP, SAP and visual

Table 4 Predictive factors of visual improvement

Variable	Visual acuity			Visual field		
	Improvement	No imp.	p value	Improvement	No imp.	p value
Age (years)	40.90 ± 10.90	47.57 ± 12.78	0.041	40.67 ± 10.97	51.18 ± 10.45	0.003
Sex (female%)	34.9%	42.9%	0.564	36.0%	36.4%	0.979
Type (functional%)	33.3%	15.4%	0.412	47.6%	9.1%	0.061
Size (mm)	24.35 ± 10.26	29.43 ± 6.54	0.022	24.31 ± 9.97	31.18 ± 7.69	0.030
Number of previous surgery						
0	95.4%	85.7%	0.093	95.4%	81.8%	0.110
1	2.3%	0.0%		2.2%	0.0%	
2	2.3%	14.3%		2.2%	18.2%	
Optic nerve atrophy	4.7%	57.1%	<0.001	4.5%	72.7%	<0.001
Pre P100 latency (ms)	107.9 ± 13.7	119.8 ± 21.2	0.007	108.1 ± 13.5	122.3 ± 23.5	0.004
Pre P100 amplitude (μV)	6.79 ± 3.48	5.92 ± 1.67	0.166	6.81 ± 3.42	5.48 ± 1.61	0.229
Post P100 latency (ms)	107.0 ± 12.6	108.2 ± 13.9	0.756	107.1 ± 12.4	108.2 ± 16.1	0.797
Post P100 amplitude (μV)	7.56 ± 3.49	5.31 ± 1.37	0.001	7.32 ± 3.41	6.35 ± 2.82	0.446
Surgical approach						
Endoscopic	86.0%	85.7%	0.973	85.4%	90.9%	0.619
Microscopic	14.0%	14.3%		14.6%	9.1%	

acuity as measures of optic nerve function. There are a few reports on the post-operative VEP changes. VEP is an objective test of visual function and does not require patient's cooperation in contrast to SAP which can be affected by these factors. Qiao et al. have previously showed that most of VEP parameters recovery happens in the first 3 postoperative months [15]. Similar pattern of VEP recovery was observed in patients with optic neuritis [12, 16]. Therefore we decided to evaluate our patients at month 3 after surgery.

Visual acuity and SAP were abnormal in 31% and 32% of eyes before surgery. P100 wave latency was significantly prolonged and P100 wave amplitude was significantly lower in abnormal eyes. VEP parameters showed statistical correlation with visual acuity and field abnormalities. Therefore, VEP test has the ability to detect abnormalities and can be used as a quantitative visual function test complementary to subjective examinations. These results are in concordance with previous studies [17–19]. The correlation between SAP and VEP has also been demonstrated in patients with optic neuritis and multiple sclerosis [12, 13]. Jayarman et al. reported the prolongation of multifocal VEP latency in the quadrant without visual field defect in SAP and suggested that VEP can diagnose chiasmal compression before any changes in conventional subjective visual field testing [18]. Thus, VEP parameters were more sensitive than the visual acuity and visual field tests and could help monitoring the progression of disease objectively in patients with normal visual acuity and field [20].

Three months after surgery the mean visual acuity and SAP score significantly improved in the affected eyes.

P100 wave latency and amplitude also improved but the differences were not significant. Larger sample size or longer follow-up duration may lead to significant results. The rapid improvement of visual function is thought to be the result of the removal of a direct physical compression on the nerves and chiasm. These results indicate that the main mechanism of axonal injury is physical blockage of signal conduction due to direct compression; whereas, delayed recovery seems to be the result of restoration of axonal transport and remyelination [15, 21].

Our study revealed that older age, larger tumor size and optic nerve atrophy are factors that lead to less improvement in visual field postoperatively. Optic nerve atrophy due to nerve ischemia could reflect high degree compression for longer duration on the optic apparatus which affected the ability of the nerve to regain normal function. Several study have demonstrated that the duration of preoperative visual symptoms could affect post-operative outcomes [22–24]. The influence of age on visual field outcomes shows conflicting results. Some studies showed the association of younger age with visual field deficit improvement [23, 25], but others reported no significant differences [26, 27].

Recently, structural measurement has been used to predict visual recovery after surgery. Retrograde degeneration following damage to the optic nerve or the optic tract leads to axonal loss in the optic nerve. Optical coherence tomography (OCT) objectively detects and quantifies retina neuronal loss. The pre-operative thickness of the retinal nerve fiber layer (RNFL) has been shown to be a predictive factor of visual recovery after tumor resection [28, 29]. Although RNFL

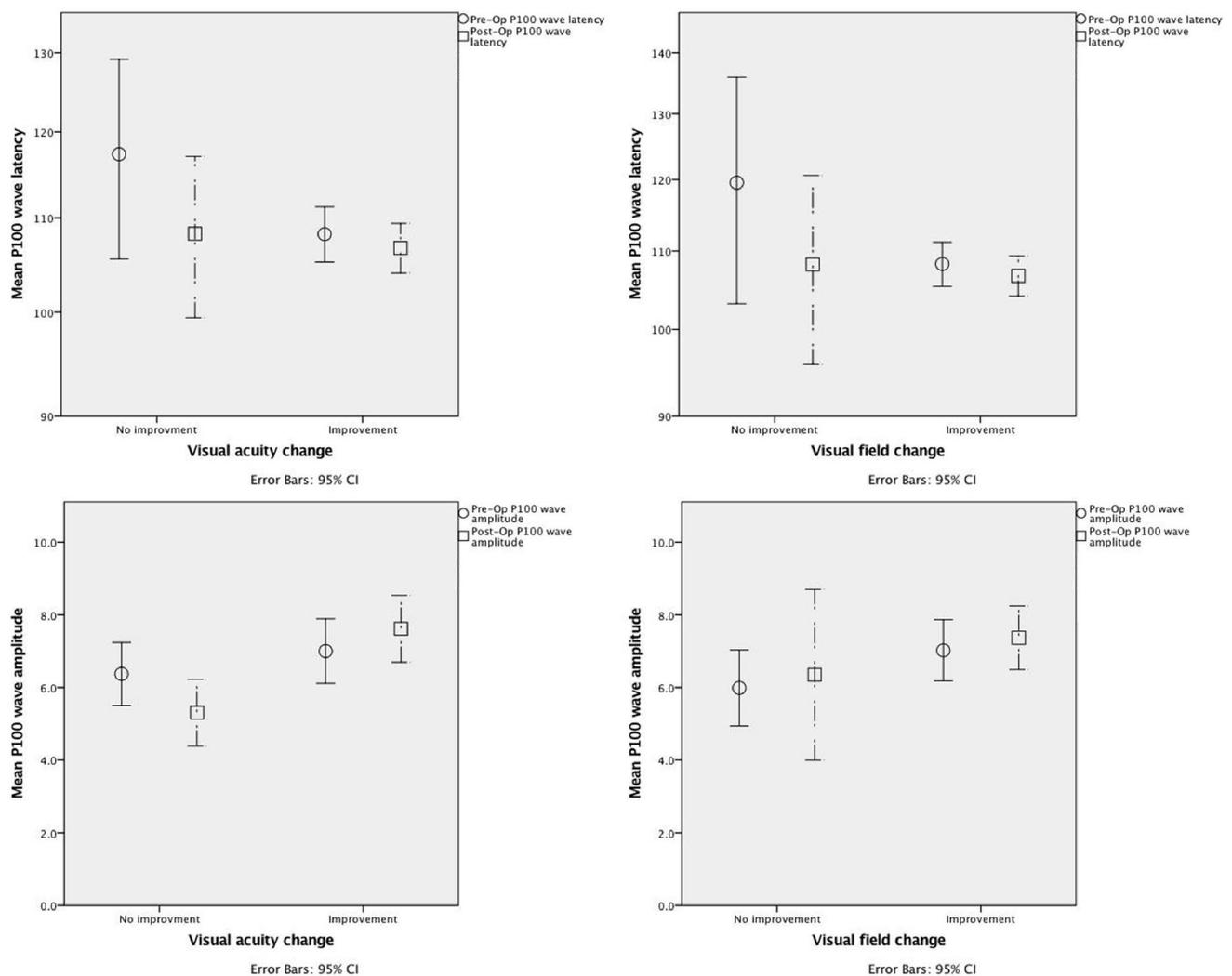


Fig. 2 VEP parameters changes in affected eyes after surgery

thickness did not improve despite visual function recovery following pituitary adenoma surgery [15, 30].

To the best of our knowledge, our study was the first study that assesses predictive value of pre- and post-operative VEP measures including P100 wave latency and amplitude in visual outcome. Patients who showed no visual improvement 3 months after surgery had significantly higher pre-operative P100 wave latency. Therefore, pre-operative P100 wave latency could be used as an objective test for prediction of visual recovery. On the other hand, electrophysiological test was more sensitive in early recognition of chiasmal compression than conventional subjective visual field testing [18, 31]. Pre-operative monitoring of VEP parameters may help to assess disease progression, and results in early treatment and optimal visual outcome despite normal visual acuity and field tests. In contrast to pre-operative VEP parameters, post-operative VEP measures were not correlated with visual improvement. Our results indicated that

VEP wave latency and amplitude improved in the group of patients who did not show visual improvement after surgery. Thus improvement of P100 wave latency and amplitude were not associated with visual recovery. In contrast to predictive value of pre-operative P100 wave latency in visual outcome, clinical value of post-operative VEP parameters is unclear. Post-operative recovery of VEP measures may predict long-term visual outcome in patients who did not experience short-term visual improvement after surgery. Therefore a study with bigger sample size, higher number of affected eyes and longer follow-up duration is needed to evaluate our conclusion.

The limitations of this study include: (1) small sample size and relatively small number of affected eyes, (2) unavailability of multifocal VEP and topographic evaluation which could have helped us to compare each quadrant separately, (3) lack of structural nerve assessment such as RNFL thickness changes.

Conclusion

VEP is a helpful quantitative and objective test which can be used complementary to visual acuity and SAP exams for assessing pre-operative visual abnormalities and post-operative visual outcome in patients with pituitary macroadenoma. There is a significant correlation between VEP, visual acuity, and SAP tests preoperatively. Patients with older age, optic disc atrophy, larger adenoma size and higher pre-operative VEP P100 wave latency are less likely to achieve visual improvement.

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