Visual evoked potentials in the assessment of patients with non-functioning chromophobe adenomas

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SUMMARY The results of visual evoked potential (VEP) examination in 34 patients with histologically confirmed chromophobe adenoma are described and discussed in relation to the clinical, radiological and surgical findings. The VEP is shown to be a reliable method of assessing the function of the intracranial visual pathways which is often more sensitive than conventional methods of examination.

The unique relationship of the optic chiasm to the pituitary gland can often lead to chiasmal compression from suprasellar extension of a pituitary tumour. Visual dysfunction is a common presenting symptom in such patients, particularly those with a non-functioning chromophobe adenoma.

Visual evoked potential (VEP) examination has previously been shown to be an accurate method of objectively assessing the function of the optic nerves and the optic chiasm, and may provide valuable information in patients with pituitary tumours.^{1–3} We present the pre-operative findings in 34 patients with histologically confirmed chromophobe adenoma and compare the neurophysiological data with that obtained from clinical examination, perimetry, radiology and surgery.

Methods and materials

(a) Patients:

The patients were all referred for investigation to the SE Thames Regional Neurosciences Unit at the Brook Hospital over a 12 year period. The criteria for inclusion in this study were histological confirmation of the tumour type with verification of its non-secretory nature and pre-operative VEP examination. Seventeen patients were male, 17 female. Mean age was 55.8 years with an age range of 25–74 years. No patient had previously received surgery or radiotherapy. The pattern VEP findings in four of the patients have been described in a previous report.²

(b) Methods of examination

All patients received a routine neurological and general medical examination. In addition, all patients had Topcon perimetry, some also having Friedman perimetry. Colour vision testing was performed with Ishihara plates. Neuroradiological assessment in all patients included skull radiography and CT. Carotid angiography was performed where indicated. Two patients seen early in the series also underwent air encephalography.

Endocrine status was assessed by measuring basal levels of growth hormone, prolactin, cortisol, luteinising hormone, follicular stimulating hormone and thyroid stimulating hormone. This was supplemented by insulin stress testing where indicated.

VEP examination was performed according to our standard techniques.^{2,4} Occipital silver/silver chloride electrodes (resistance less than 5 k ohms) were situated 2 cm anterior and 2 cm lateral to theinion recording in relation to ipsilateral sylvian and parietal electrodes according to the Modified Maudsley system of electrode placement.² Full field pattern reversal stimulation was provided by a moving mirror stimulator subtending a total field at the eye of 11° with an individual check size of 26'. Mean luminance was 400 cdm⁻² with a contrast of 89%. The VEP amplitude obtained using these stimulus parameters is maximal with the electrode positions described. If the available stimulus subtends a much larger field with larger checks the maximal amplitude is obtained with the more anteriorly and laterally placed electrodes recommended by other authors.^{1,5} Additional stimulation was often performed with 13' checks contained in an 8° field. Monocular stimulation of each eye was performed at least twice to ensure result reliability. Spectacle correction was worn where appropriate. Most patients also received diffuse flash stimulation. In more recent years pattern electroretinography (PERG) was often performed. The techniques for this have been described elsewhere.⁶

Surgical approach to the pituitary fossa was either sub-frontal through a right or left craniotomy or by a transsphenoidal route. Histological examination of the tumour included

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haematoxylin and eosin stains in addition to PAS orange-G. Immuno-peroxidase studies were also undertaken.

Results

(a) Presentation and clinical examination

Visual failure or disturbance was the main presenting symptom in this series, and the sole reason for referral in 29 of the 34 patients. The visual symptoms were predominantly unilateral in 20 of these 29 patients. Headache was a feature in 10/34 patients, particularly in the period immediately prior to presentation. One patient presented with pituitary apoplexy. In two patients there was a recent history of epilepsy.

Three patients with hypopituitarism were found to have visual field defects while being investigated for impotence, tiredness and depression. One patient was found to have an enlarged pituitary fossa on skull radiographs while being assessed following a head injury, and in one patient being investigated for dementia, a pituitary tumour was found on CT. Both of these latter patients had bitemporal hemianopia and disc pallor on closer examination.

Eight patients had been misdiagnosed prior to neurosurgical referral. In six patients visual loss had been ascribed to macular dysfunction (two patients), retrobulbar neuritis, glaucoma, hypertension or migraine. In the other two patients the visual loss had been attributed to cataracts.

There was a mean duration of visual symptoms of 16 months prior to diagnosis with a range from 1 week (the patient with pituitary apoplexy) to 4 years. Some patients had suffered a rapid deterioration in vision (without apoplexy) after being kept under review for several years.

(b) Visual fields and visual acuities

The visual field defects at presentation to this unit are shown in the table. The visual acuities are displayed in fig 1. It is noted that six patients had one eye with vision worse than 6/60 at the time of neurosurgical referral, and in one of these patients the more severely affected eye had deteriorated to "no perception of light". The patients with central visual field loss had the more severe reductions in acuity. Severe defects in colour vision were also associated with loss of central

Table Visual field defect at time of neurosurgical referral

Symmetrical bitemporal hemianopia	12
Asymmetrical bitemporal hemianopia	6
Asymmetrical bitemporal hemianopia with paracentral scotoma	4
Bitemporal superior quadrant loss	2
Bitemporal superior quadrant loss with paracentral scotoma	2
Unilateral superior quadrant loss	2
Congruous homonymous hemianopia	2
Severe generalised loss in one eye with temporal field loss in the other	4

Fig 1 Visual acuities at presentation in 68 eyes of 34 patients with non-functioning chromophobe adenomas.

visual field. Nine patients had an unequivocally normal fundal appearance in both eyes, despite a mean duration of visual symptoms of 13 months. The presence of an afferent pupillary defect was associated with severe visual loss.

(c) Endocrine status

The characteristic features of hypopituitarism were evident on examination in 12 patients. All 34 patients required long term replacement therapy after surgery.

(d) Radiology

The pituitary fossa showed marked expansion and erosion on skull radiographs in 33/34 patients. CT revealed that the tumour extended superiorly in the mid-line in 20 patients, often up to and indenting the third ventricle, but not causing hydrocephalus. The suprasellar extension was asymmetrical in 11 patients, being more marked on the left in nine patients. The plain skull radiographs in these 11 patients had shown correspondingly asymmetrical expansion of the

Fig 2 Magnitude of monocular pattern VEP latency delays as measured in the traces derived from the ipsilateral hemisphere. See text for further details.

Fig 3 Pre- and post-operative pattern VEP findings in a 38 year old male. The broken vertical line indicates the upper limit of normal major positive component latency. The pre-operative right eye (OD) findings are of abnormal latency in the left hemisphere traces but right hemisphere recordings fall within the normal range. The left eye (OS) pre-operative findings are grossly abnormal over both hemispheres, worse in the right hemisphere. These results indicate left optic nerve and chiasmal dysfunction but no right optic nerve dysfunction is suggested. The post-operative recordings from OD are completely normal with no significant interhemispheric asymmetry. The post-operative OS findings also show marked improvement; the interhemispheric asymmetry is no longer present and the major component latency falls within the normal range. The magnitude of the interocular asymmetry does however fall 3 SD outside the normal range suggesting probable residual left optic nerve dysfunction. Note the differences in calibration.

Fig 4 Pre- and post-operative pattern VEP findings in a 50 year old male. The left eye (OS) major positivity is delayed in the traces from both hemispheres with an additional right hemisphere amplitude reduction. Right eye recordings are of abnormal latency in the left hemisphere traces. This combination suggests left optic nerve and chiasmal dysfunction. The borderline abnormal latency from the right eye in the right hemisphere traces suggests possible additional right optic nerve dysfunction. Findings from both eyes are much improved following surgery.

Fig 5 Pattern VEP findings in a 26 year old female. Left eye PVEP is extinguished. Right eye PVEP is markedly delayed (20 ms outside the upper limit of normal for age) in the right hemisphere traces with an almost abolished response over the contralateral hemisphere. See discussion for clinical details.

pituitary fossa. In three patients CT showed massive growth of the tumour with spread into the middle cranial fossa. Marked suprasellar extension on CT without gross changes on the plain skull radiograph occurred in only one patient.

(e) Visual evoked potentials

Analysis of the pattern VEP centred on the major positive component at approx. 100 ms (P100). The latency of this component was measured in the traces corresponding to each hemisphere according to our standard techniques.²⁷ It has previously been demonstrated^{24,7} that the recording techniques described do not result in the "paradoxical lateralisation" described by other authors using different stimulus and recording parameters.¹⁵ Onset and offset amplitudes of the P100 component were measured from both hemispheres. In addition the latency of the preceding (N75) and following (N135) negative components were also examined. Flash response measurements focused on the major positive component at some 120 ms with particular regard to the presence of interocular or interhemispheric asymmetries. A normal VEP can be seen in the post-operative findings of the patient shown in fig 3.

The normal values for our laboratory are based on a mixed age group of more than 100 subjects, the upper limit of normal latency (mean + 3 SD) being age dependent but in the region of 106 ms. An interocular or interhemispheric latency asymmetry of 6 ms or greater is abnormal (mean + 3 SD). An interocular or interhemispheric amplitude asymmetry of 50% or greater is abnormal. The abnormal interocular and interhemispheric values are similar for the flash VEP.

The principal abnormality present in the patients was a "crossed" asymmetry where the abnormality is maximal over the hemisphere contralateral to the stimulated eye, that is, changes over the left hemisphere on right eye stimulation and vice versa. Latency

changes in the ipsilateral hemisphere traces were frequently seen indicating probable optic nerve dysfunction (fig 2).² An interhemispheric asymmetry which is similar for the two eyes ("uncrossed") indicates retrochiasmal dysfunction.⁴

Typical VEP findings are shown in figs 3, 4 and 5. The CT scan of the patient in fig 5 is shown in fig 6.

In none of the 34 patients was VEP examination completely normal. Thirty patients had binocular abnormalities in the VEP, only four patients showing a purely unocular VEP abnormality. A normal pattern VEP was found in four eyes.

There was a pattern VEP abnormality in 30 eyes which was approximately symmetrical over the two hemispheres but in five of these the magnitude of the interhemispheric asymmetry was borderline. One additional eye had a borderline abnormal latency. Sixteen eyes showed an abnormality over the ipsilateral hemisphere which was significantly worse over the contralateral hemisphere. Seven eyes showed only contralateral abnormalities, the ipsilateral hemisphere traces falling within the normal range. Two further eyes had a normal ipsilateral response with a borderline abnormal contralateral response. In five eyes a definite contralateral abnormality was only seen with the 13' check pattern. In a further three eyes the contralateral abnormality was confined to the N135 component.

When the ipsilateral findings are considered, that is, principally assessing optic nerve function, three patients showed no ipsilateral pattern VEP abnormality; 15 patients showed unocular abnormalities and one further patient showed a definite unocular abnormality with a borderline abnormality in the other eye; the other 15 patients all had abnormalities in the VEPs from both eyes.

Two patients had abnormal flash VEPs but normal pattern VEPs from one eye. Both had superior temporal quadrant field defects in the affected eyes. Two more eyes had normal pattern VEPs; in one the visual

Fig 6 CT scan of the patient in fig 5. The asymmetrical nature of the tumour is clearly shown.

field was full, in the other there was a paracentral scotoma. This latter eye is the only eye in the series in which clinical testing suggested dysfunction which was not also suggested by the VEP.

(f) VEP and clinical assessment of visual function

There was good correlation between the presence of a visual field defect and a pattern VEP abnormality, all other eyes (62/62) with clinical visual field defects having abnormal VEPs. Two patients had eyes with full visual fields in which the pattern VEP was abnormal. Both patients in whom the VEPs showed an uncrossed asymmetry had homonymous visual field defects.

There was poor correlation between visual acuity and the VEP findings. There were 14 eyes in 10 patients in which the visual acuity was normal (6/9 or better) but in which the pattern VEP was definitely abnormal. Two of these eyes had latency delays in excess of 40 ms. Indeed, many eyes in the present series had marked latency delays. The range of abnormal latency values is shown in fig 2.

Fundal appearance similarly correlated poorly with the VEP findings. There were nine patients with definitely normal fundi in whom the VEPs were

abnormal. In eight patients the VEP abnormality was unocular, the ninth patient having abnormalities in both eyes. All patients with optic atrophy had abnormal VEPs, usually grossly abnormal.

(g) VEP, radiology and surgical findings

The correlation between radiological findings and the VEP changes was still less marked. In 20 patients CT suggested a mid-line suprasellar extension but the VEPs in these patients were markedly asymmetrical. In two patients with asymmetrical extension on the CT scan it was the optic nerve contralateral to the side of maximum extension which was suggested by the VEP to be more severely affected. At craniotomy, the VEPs were found to have accurately predicted the site of maximum distortion of the optic nerves by the tumour. VEP and radiological findings were compatible in the other patients.

Surgery was performed through a right frontal craniotomy in 10 patients; a left sided approach was used in six patients. Asymmetrical involvement of the optic nerves and chiasm was found in each case that underwent craniotomy, and was in keeping with the VEP findings. Transsphenoidal surgery was performed in the other 18 patients.

Discussion

The clinical characteristics of the 34 patients in this series are typical of those patients with large non-functioning tumours.^{8,9} Most patients were elderly, presented with visual symptoms and had visual field defects. Many had complained of visual symptoms for a considerable period prior to diagnosis, and it is of interest that the 17 patients above 60 years of age had an average of 2 years between onset of symptoms and diagnosis, whereas those younger than 60 had an average delay of only one year. It is notable that 20/34 patients presented with visual failure that was predominantly unilateral. The classical bitemporal hemianopia was present in only 12/34 patients.

Previous extensive series^{9,9} report similar patterns of visual field and acuity loss, but these studies did not have access to modern endocrine testing and it is therefore difficult to assess how many of the patients previously described as having a "chromophobe adenoma" could be properly described as having non-functioning tumours.

Previous VEP studies of patients with pituitary tumours have reported limited numbers of patients and poorly defined patient groups. The largest study to date³ reported the findings in 83 patients but only 12 of these patients had abnormal VEPs with suprasellar extension of the tumour. Haimovic and Pedley¹⁰ described the findings in 14 pituitary adenomas. Stark and Lenton⁷ reported 13 patients, but there was only histological confirmation of tumour type in four patients. Halliday and colleagues¹ described the VEP findings in eight patients with pituitary tumours, but in addition reported five patients with craniopharyngioma or suprasellar meningioma. Holder² reported 10 patients with chiasmal compression, but in two patients this had resulted from a craniopharyngioma or an aneurysm.

The principal abnormality found in previous series was a "crossed asymmetry" that is the potentials generated in the hemisphere contralateral to the stimulated eye show the maximum abnormality. The VEP registration techniques used in the present study do not result in the "paradoxical" lateralisation described with large field/large check stimuli and more anteriorly and laterally placed occipital electrodes,¹¹ but are otherwise fully comparable. Each technique is internally consistent and an efficient way of assessing the intracranial visual pathways, but it is essential that each laboratory standardises its techniques according to preferred method, paying particular attention to the importance of stimulus parameters.^{6,11,12}

Some authors^{5,13-16} advocate the use of hemifield stimulation to enhance the abnormality, but there are technical difficulties with regard to fixation in patients with reduced acuity which can render this type of

stimulation difficult to perform accurately in all patients. Patient concentration also has to be extremely high to achieve satisfactory results with half-field stimulation, and this may not always be present in the elderly patients which form a large proportion of those with non-functioning pituitary tumours.

The findings in the present series are consistent with those of previous authors, the VEPs usually showing a "crossed" asymmetry indicative of chiasmal dysfunction. All 34 patients had abnormal VEPs when both pattern and flash stimulation were taken into consideration.

The value of the VEP is demonstrated by the comparisons between the electrophysiological data and the results of clinical examination and perimetry. There was often a delay in the VEP despite normal visual acuity, in keeping with the findings of previous authors.^{1,3,5} VEP abnormalities were also observed in eyes with full visual fields, again confirming previous findings.^{3,5,10} Only one eye of the 68 studied had a normal VEP in the presence of a visual field defect (a small paracentral scotoma). When the visual fields are directly compared with the VEPs, the VEPs often suggested a greater degree of dysfunction than the fields. Some patients, once diagnosed, decline surgery or are kept under review (4/34). One patient in this series was initially diagnosed three years prior to surgery. Follow-up during this period was with routine clinical testing but not serial VEP recording. The visual acuity in one eye immediately prior to surgery had only fallen from 6/6 to 6/12, but the VEP, which had previously shown only a mild latency delay, was virtually extinguished. Overall the VEP was a more sensitive indicator of visual pathway dysfunction than the conventional techniques of visual acuity and perimetry.

The comparison between the VEPs and the CT scans, which assess structure not function, indicates that the VEP often suggested functional asymmetry where the scan demonstrated a symmetrical mid-line lesion. The functional assessment provided by the VEP may then influence the surgical approach.

Many authors¹⁶⁻¹⁸ have emphasised the difficulties in the diagnosis of pituitary tumours, stressing that many patients present with unioocular symptoms. An atypical retrobulbar neuritis may be diagnosed in the younger patient. This occurred in one of our patients who initially presented with a scotomatous visual field defect, the correct diagnosis being suspected when the second eye developed temporal visual field loss. The VEP at this stage (fig 5) showed severe chiasmal dysfunction but had not been performed at initial presentation. The "crossed asymmetry" found in the VEPs of patients with chiasmal compression is a rare occurrence in demyelination. Furthermore a favoura-

ble response to steroid therapy should not be considered a definite indicator of demyelination as this has been described with a pituitary tumour.¹⁹

The misdiagnosis of patients with chiasmal compression may result in severe irreversible visual loss. Ocular pathology is a frequent incidental finding in the elderly which may contribute to the difficulty of diagnosis in this age group. Electrodiagnostic testing is now capable of a complete assessment of the visual pathways,²⁰ recent advances in pattern electroretinography⁴ enabling us to distinguish those patients with optic nerve dysfunction from those with more distal problems such as cataract, macular degeneration etc. To make the correct diagnosis in the patient in whom chiasmal dysfunction is suspected, it is essential that examination includes measurement of visual acuity, visual fields to a red target, skull radiograph and CT scan. The results of the present study confirm that the VEP, with its sensitivity and objectivity, is a valuable addition to this routine.

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