Event related potentials recorded in patients with locked-in syndrome

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Abstract

Objective—To determine the possibility of recording “cognitive” event related potentials (ERPs) in locked-in patients and therefore to determine whether ERPs can have a role in differential diagnosis of coma.

Methods—ERPs to classic auditory or visual ‘‘odd ball paradigms’’ were recorded three to four days, seven to eight days, and 30 to 60 days after admission to the intensive care unit, in four patients affected by basilar artery thrombembolism resulting in locked-in syndrome. Two patients (one 32 year old man, one 31 year old woman) could move the eyes laterally and vertically spontaneously and on command. One patient (a 39 year old man) had a ‘‘one and half syndrome’’, one patient (a 40 year old woman) could only elevate the left eyelid and eye. Results were compared with data from 30 age matched controls. In the last recording session a letter recognition paradigm was applied, in which ERPs were produced by the identification of letters forming a word. Results were compared with five age matched controls. Brainstem lesions extending to the pontomesencephalic junction were found on MRI and CT.

Results—ERPs to the oddball paradigms were recorded in three patients in the first recording session, in all patients in the second recording session. Latency, amplitude, and topographic distribution of ERP components were inside normal limits. With the letter recognition paradigm the patients could emit a P3 component to correspond with target letters, with the same margin of error as controls.

Conclusion—It is possible to record ERPs in patients with locked-in syndrome shortly after the acute ischaemic lesion, and therefore to assess objectively cognitive activities. Furthermore the letter recognition paradigm could be implemented to facilitate linguistic communication with patients with locked-in syndrome.

Case reports

Patient 1
Patient 1 was a 32 year old man, a professional cook, 172 cm in height, 68 kg weight, a non-smoker, with a negative medical history. He arrived at the emergency unit of our hospital because of headache followed by “abnormal vision” and numbness of the right arm and leg. Blood pressure was 200/120 mm Hg at admission. Within 12 hours he became stuporous, anarctic, and tetraparetic with bilateral Babinski signs, he had two generalised tonic-clonic seizures, painful stimuli induced decerebrate posturing, and lateral eye movements. The first CT was reported as negative. He received 20 000 units of heparin in 24 hours. He developed central hyperventilation (frequency 40-50/ min, PO2 85-90 mm Hg, PCO2 25-40 mm Hg).
He was intubated and artificially ventilated and treated with 2 mg/kg/h thiopental. His CSF was normal. Within three days it was possible to interrupt artificial ventilation and he underwent tracheotomy. A new CT showed a caudal pontine ischaemic lesion, prominent on the right side. The patient was then awake. Painful stimuli induced blinking and decerebrate posturing and he could blink and move the eyes laterally and vertically spontaneously and on command. He understood verbal commands and spasmodic laughing or crying was elicited by appropriate stimuli. An EEG showed posterior 9-10 Hz rhythms, disappearing on eye closure, and sporadic synchronous 5-6 Hz sequences lasting for one to two seconds. During sleep, slow activity, K complexes, spindles, and vertex waves were recorded. MRI showed a paramedian (right) area hypointense in T1 weighted images and hyperintense in T2 images (fig 1).

**PATIENT 2**

Patient 2 was a 39 year old man, a library clerk, 175 cm in height, 81 kg weight, previously affected by “basilar artery migraine”. He arrived at the emergency unit of our hospital because of headache and right brachiocephaloparesis. The first CT was reported as normal. The first EEG showed posterior α rhythms unresponsive to stimuli. He was treated with 20 000 units of heparin intravenously, but he became tetraparetic and stuporous, with ataxic breathing. He was intubated and artificially ventilated; within five days it was possible to interrupt artificial ventilation and he underwent tracheotomy. The patient was then awake. Painful stimuli elicited blinking and decerebrate posturing, he could move his eyes spontaneously and on command vertically and to the left with a contralateral “one and a half” syndrome. He laughed and cried spasmodically. A second CT showed a caudal pontine ischaemic lesion. An EEG showed posterior 10-11 Hz rhythms, disappearing when his eyes were closed. Slow activity, K complex, spindles, vertex V waves, and REM desynchronisation were seen during sleep. Brain MRI confirmed the paramedian area, which was hypointense in T1 weighted images and hyperintense in T2 images (fig 1).

**PATIENT 3**

Patient 3 was a 40 year old woman, a housewife, obese (163 cm in height, 91 kg weight), with a negative medical history. She was admitted to the surgery of our hospital because of acute abdominal pain, ileus, and suspected mesenteric artery thrombosis. She became stuporous and tetraparetic, with ataxic brainstem dysfunction.
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breathing, and underwent tracheotomy and artificial ventilation. An EEG showed posterior 
\( \alpha \) rhythms, unmodified by stimuli. The first CT showed hypointensity in pontine structures; haematological studies showed platelet decrement and increment of fibrinogen degradation products. She was treated with 20 000 units heparin daily.

Within three days she was awake. She could elevate the left eyelid and the left eye spontaneously and on command and EEG showed 10-11 Hz \( \alpha \) rhythms and normal sleep patterns during sleep. Painful stimuli elicited spasmodyc crying and decerebrate posturing. She developed left femoral vein thrombosis. A new CT showed the hypointense lesions of the pons, and repeated MRI (fig 1) confirmed earlier findings. She was found positive for antiphospholipid antibodies.

**PATIENT 4**

Patient 4 was a 31 year old housewife, normo-
type (166 cm in height, 56 kg weight). She underwent a caesarean section due to initial gestosis, with delivery of a normal baby. She was somnolent-stuporous for three days and she was then transferred from the obstetric division of a nearby hospital to our department. At the first neurological examination she was found to be tetraplegic, but in a waking state. She was able to blink and move her eyes vertically, spontaneously and on command. Brain CT showed hypointensity of the caudalpons, left hypointensity of the rostral pons, and bilateral hypointensities of the cerebral peduncles (fig 1). The first EEG showed 9-11 Hz \( \alpha \) rhythmic activity, disappearing when her eyes closed, and normal sleep patterns. She was intubated and artificially ventilated for six days. Thoracic expansion than returned to normal. Ten days after admission to our department she had left hemiplegia, right hemiparesis (she could lift her left arm), facial diplegia, and tongue protrusion. Three months after rehab-
ilization therapy she could walk with the aid of a frame.

**Methods**

ERPs to the auditory and visual oddball para-
digms were recorded three to four days after admission to the intensive care unit of our University, when the patients were artificially ventilated, seven to eight days later, when arti-
ficial ventilation could be discontinued and patients could be transferred to our neurology department, and 30 to 60 days later when patients were transferred to a rehabilitation unit. The letter recognition paradigm was used only in the last recording session. The ERPs were recorded according to methods described in detail elsewhere.  

**Letter recognition paradigm**

The letter recognition paradigm was developed as a simplification of the “mental prosthesis” paradigm introduced by Farwell and Donchin. Stimuli were grey letters subtending 5° visual angles, presented on the same pattern generator screen used for the or-
ientation “odd ball paradigm”. Luminance of the blank screen and the screen surrounding the letters was 75 cd/m\(^2\), luminance of the let-
ters was 32 cd/m\(^2\). Letters of the alphabet were presented randomly for one second on the screen. In the first recording session (template definition) five healthy controls, 30-43 years old, were asked to discriminate between letters forming the word “video” and other letters; the target letters were to be recognised only when presented in the appropriated sequence. The EEG was recorded from 15 scalp derivations (Fp1-2, F7-8, and T3-4 were excluded, one EOG channel was included), with 0.5-70 Hz band pass filtered and at a 1000 Hz sampling rate. Data were stored on the computer hard disk. Responses to target and non-target stimuli were averaged off-line. The averaged response to target stimuli was used to define “template” characteristics, with the ESAOTE shape detection program, based on a time win-
dow (290-500 ms), slope of the descending (0.15-0.4 mV/ms) and ascending limb (0.1-0.3 mV/ms), and minimum duration of descending-ascending positive deflection (70-110 ms).

In the second recording session each control was asked to select letters forming a word from the letter sequence presented on the screen, in five sets of six minutes each. The P3 template obtained in the first recording session in each control was used to compute the covariance of single responses to letter presentation with this
template. The values obtained from this analysis were then used to determine the letter on which the subject was focusing attention. This same letter recognition paradigm was used in the last recording session. All four patients were initially asked to blink or elevate the eyelid when they understood the task. The letter sequences with the predefined target (“video”) were then presented for 15 minutes and the template was obtained for each patient. In the second part of the paradigm 370-600 acquisitions were stored on the hard disk in 30 minutes and compared with the template. Attended letters were 45-72.

Results

Figure 1 shows the ischaemic lesion involving the caudal pontine area, prominent on the right.

The ERPs to the auditory and visual oddball paradigms were recorded in the first session in patients 2, 3, and 4 and in the second and third session in patient 1. They consisted of a “normal” N1-P1 sequence to frequent non-target stimuli, and N1-P1-N2-P3 components to target stimuli (fig 2). Latencies, amplitudes, and scalp distributions of ERP components were within normal limits. The table reports mean values of age matched controls and results obtained in each patient. Significance probability mapping with Z transformation was performed as a comparison between age matched maps and maps of each patient, and did not show any Z value above or below 2 SD in any of the scalp derivations. Paired Wilcoxon tests of N2 and P3 amplitude or latencies did not show any significant increment or decrement in the three recording sessions for patients 2, 3, and 4 and in the two recording sessions for patient 1. The test-retest reliability of P3 in patients with locked-in syndrome was 0.81-0.88, not different from controls (0.81-0.91). Figure 2 shows ERPs recorded with the visual or auditory oddball paradigm in the three patients.

The letter recognition task elicited positive P3 components to attended letters in all patients and controls. The averaged responses obtained during the template definition task consisted of N1 components recorded from Cz, Pz, P3, P4, O1, O2, and Oz leads to attended and unattended letters. N1 peaked at 120-185 ms, the amplitude (measured from Pz) was 12.2 (SD 3.6) µV in patients and controls. A following peak, P2 was recorded also from central and frontal derivations, latency was from 182 to 260 ms. Only attended letters elicited N2 (272-336 ms, amplitude 4.2 (SD 2.8) µV from Pz) and P3 on Cz, C3, C4, P3, Pz, P4, O1, O2, and Oz leads (348-452 ms). The mean P3 latency was 408 (SD 18.5) ms in controls, 411 (SD 17.2) ms in the four patients. The mean amplitude from baseline, recorded from Pz, was 7.7 (SD 2.1) µV in controls and 8.1 (SD 3.00) µV in patients. A Student’s t test comparison with the five controls was not significant. The template (shape detection program) obtained from
findings with other electrophysiological techniques that could only show normal or abnormal afference of sensory pathways, ERPs can evidence an ongoing cognitive activity, and thus confirm the integrity of some brain functions. The utility of ERP recording might seem overstated if only classic descriptions of locked-in syndrome are considered—that is, with integrity of ocular movements—thus implying that patients can communicate with eye movements. As we report in our description, however, eye movements can be severely altered in patients who are otherwise capable of complex cognitive activities (patient 2 had a one and half syndrome, patient 3 could only elevate one eye and one eyelid), and previous literature already described cases of complete (“mesencephalic”) locked-in syndrome in patients incapable of eye movements. The involvement of eye and lid movements in our patients prompted the second part of our study, based on the letter recognition paradigm. In two of our patients the “augmentive communication systems” such as the ETRAN board or the words + infrared switch, that were developed for patients with amyotrophic lateral sclerosis could not be used because of impairment of eye movement. We therefore tested the feasibility of the mental prosthesis project proposed by Farwell and Donchin. We showed that ERP to a letter recognition paradigm can be recorded in patients with locked-in syndrome; and therefore that the mental prosthesis project might be feasible. Obviously the method used in our patients cannot have any practical application, because attended letters can be related to ERPs only after the acquired EEG activity is analysed off line with the template shape detection program, but further developments of on line EEG analysis systems might be able to overcome the technical problems.

A final comment relates to some of the current hypotheses on P3 generators. As reported in the introduction, some authors think that a trigger of P3 activity might be located in the thalamus or in brain stem structures. One of the generators might correspond to the cholinergic neurons of the tegmentopontine area that constitute the trigger of widespread electrocortical activities. In our patients we showed, however, that ischaemic lesions were extended to the tegmental pons (fig 1): as P3 had normal latencies and amplitudes in these patients, we suggest that a P3 generator located in tegmentopontine areas is unlikely and, therefore, that any P3 generator must be located more rostrally.

**Discussion**

Although many studies have been published on the electrophysiological assessment of the locked-in syndrome, ERP recordings have never been described before. In our paper we show that ERP components could be detected in all four locked-in patients, with three different cognitive paradigms. In patient 1, ERPs could not be recorded in the first recording session, probably because the initial reversible ischaemic lesion was extending rostrally to the pons.

As ERPs were recorded also during artificial ventilation in at least three patients, we suggest that the recording of ERP to the simple classic auditory oddball paradigm could become a useful tool in the evaluation of locked-in syndrome. Compared with the heterogeneity of averaged responses to attended letters could detect 67%-100% of P3 to attended letters in the rerun of the 30 minute acquisition during the second part of the paradigm. False positives were 10%-28% of detected P3s. Sequences of letters forming words could be detected with a 9%-43% margin of error (false positives, false negatives), single words (“hunger”, “tired”, “stupid” in italian) could be identified every 1.5-3.5 min. A χ² comparison of detection errors did not show differences between patients and controls. Figure 3 shows a sequence of single responses obtained in patient 4 during the second part of the letter recognition paradigm.
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