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Auditory Brain-Stem and Middle- and Long-Latency Evoked Potentials in Coma

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• **Twenty-five patients in coma, each with a Glascow Coma Scale measure less than or equal to five, were studied within the first three days of hospitalization with auditory brain-stem and middle- and long-latency evoked potentials. Survival was related to the simultaneous preservation of long- and middle-latency and brain-stem evoked potentials. The preservation of just middle-latency and/or brain-stem components did not correlate with survival. However, if the group of patients in coma due to head trauma was analyzed separately, survival could be related to the results of the brain-stem evoked potentials. There was no relationship between survival and the results of the initial clinical neurological examination. In patients who survived, there was no pattern of evoked potential preservation that related to the quality of survival.**

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An auditory stimulus elicits a series of potentials lasting several hundred milliseconds that can be recorded from the scalp of humans using computer averaging techniques.[1] The potentials are classified according to their latency of occurrence (early, <15 ms; middle, 15 to 50 ms; and long, >50 ms), presumed site of generation (early from the brain stem, middle and long from the cerebrum), and relative sensitivity to the physical features of the stimulus (exogenous potentials) or to the mental state of the subject (endogenous or cognitive potentials).[2] The ability of evoked potentials to monitor the physiological state of the auditory system at several different levels of the nervous system has led to their application to patients in coma due to head trauma. These studies suggest that the presence of some of these auditory potentials correlates with survival from coma due to trauma.[3-5] The present study was undertaken to assess further the relationship between auditory evoked potential measures and survival in patients in coma due to a variety of causes. The patients were profoundly unresponsive, with a Glascow Coma Scale rating of five or less, indicating a poor prognosis for survival.

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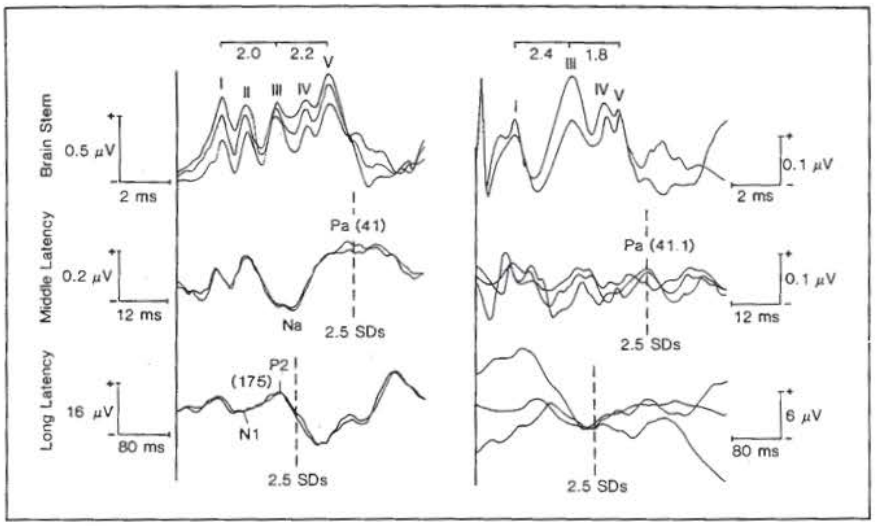
METHODS

Twenty-five comatose patients ranging in age from 14 to 84 years (mean, 43 years) were studied. The causes of coma were various, including anoxia (13 patients), trauma (six patients), vascular (three patients), hepatorenal failure (two patients), and acute hydrocephalus (one patient). All patients were examined neurologically with regard to respirations, pupillary responses, extraocular motility, and motor behavior. Their level of function was greatly depressed, as evidenced by their rating on the Glascow Coma Scale of five or less. Auditory evoked potentials were recorded at least once in all of the patients at a mean of 3.4 days after the onset of the coma. In nine patients, the potentials were recorded a second time. Sixteen of the patients also had an EEG performed close to the time of the evoked potential studies.

Auditory evoked potentials were measured between an electrode on the vertex and an electrode on the ear ipsilateral to the ear stimulated. Monaural stimulation of both ears was performed. Duplicate averages were obtained to ensure the reliability of identifying the evoked potential components. An artifact reject algorithm was used to eliminate individual trials contaminated by high-amplitude muscle activity. Auditory brain-stem potentials were elicited by rarefaction clicks produced by activating earphones with a 100-μs pulse at an intensity of 100-dB peak sound pressure level (SPL). The stimulus rate was 11.1/s and 2,000 trials made up the average. The recording filters were 150 to 3,000 Hz. Auditory middle-latency potentials were elicited with 1,000 presentations of a 30-ms duration 1,000-Hz tone burst (3-ms rise/fall times) presented at a rate of 11.1/s at an intensity of 71.5-dB SPL. The recording filters were set from 30 to 250 Hz. Auditory long-latency potentials were elicited with 100 trials of the same tone burst. The stimulus rate was 0.7/s, and the recording filters were set from 1 to 30 Hz.

Auditory brain-stem potentials were classified as abnormal if the following occurred: (1) the interpeak latencies were 2.5 SDs beyond the mean value (2.5 ms for I-III, 2.2 ms for III-V, and 4.5 ms for I-V); (2) waves III or V were not present; or (3) the amplitude ratio of IV-V/I was less than 0.5. The auditory brain-stem potentials were classified as absent when there were no reproducible components beyond wave I. Middle-latency evoked potentials were classified as abnormal if the positive component, Pa, was beyond 40 ms (>2.5 SDs above the mean) and absent when no reproducible components (Na, Pa, Nb) were seen. Long-latency evoked potentials were abnormal when the positive component, P2, occurred beyond 190 ms (>2.5 SDs above the mean) and absent if components N1 and P2 were not reproducible. The evoked potentials were usually comparable from stimulation of each ear. In 18 patients, the brain-stem components were the same from stimulation of either ear; in 20 patients, the middle-latency potentials were the same from stimulation of either



Auditory brain-stem and middle- and long-latency potentials from normal subject (at left) and from patient in coma following anoxia (at right). Values of I-III and III-V intervals are indicated above brain-stem potentials, and in both subjects, these values as well as I-V interval and I/V amplitude ratio are normal. The 2.5 SDs of upper limit of latency value for normals for both Pa component of middle-latency potentials and P2 component of long-latency potentials are indicated by vertical dashed lines. Note that Pa component is within normal range in patient, whereas no reproducible components could be identified in long-latency range. Amplitude calibration scale for patient is approximately one half of that for normal subject.

ear; and in 22 patients, the long-latency components were the same from stimulation of either ear. The results from stimulation of the two ears were sorted as follows: normal indicated that the test results from both ears were normal; abnormal meant that the potentials from at least one of the ears were abnormal; and absent meant that no evoked potentials could be identified from both ears. The Figure contains examples of a set of auditory brain-stem and middle- and long-latency evoked potentials from both a normal subject and one of the patients in coma.

The incidence of survival among the 25 patients varied according to the cause of their illness: anoxia (three of 13 patients); trauma (four of six patients); vascular diseases (one of three patients); hepatorenal failure (one of two patients); and hydrocephalus (zero of one patient). There were three patients who recovered from coma but died of secondary problems and were thus classified as survivors: one with an anoxic insult who experienced a cardiopulmonary arrest while receiving dialysis after three weeks in a vegetative state; one with head trauma who died of pneumonia after recovering from coma to a vegetative state for one month's duration; and one with a subarachnoid hemorrhage who survived one month in a vegetative state before dying of pneumonia.

RESULTS

All of the patients with long-latency components (n = 9) also had middle-latency and brain-stem components preserved. Six of these patients survived. There were five patients without long-latency components but with middle-latency and brain-stem potentials preserved, of whom two survived. In contrast, of the eight patients with only auditory brain-stem potentials present, just one survived, while none of the three patients without any of the evoked potentials survived. Combining the patients without any evoked potentials and those with only the brain-stem components into a single category and then comparing the difference in survival between the three patterns of evoked potential preservation disclosed a significant difference (Table 1; $P < .01$).

Analysis of the results in Table 1 yields the following conclusions: absence of auditory brain-stem potentials in a comatose patient is a reliable indicator that the patient will not survive (zero of three patients). However, the converse statement that the presence of just auditory brain-stem potentials predicts survival was not confirmed (one of eight patients). The correlation between the preservation of long-latency components and survival (six of nine patients) is only weakly positive. However, this correlation is improved if details of the hospital course of the three patients with preserved long-latency components who died are considered. In all three patients, the long-latency potentials were measured early during the evolution of their illness. The first patient had coma develop from hepatorenal failure following the induction of anesthesia with halothane. The initial set of potentials was recorded later that same day when the serum ammonia level was 144 mEq/mL. Three days later, the serum ammonia level had risen to 7,200 mEq/mL, and no evoked potentials could be defined. The patient died the following day. The second patient took an overdose of tricyclic drugs and had anoxia for an indeterminate period. The initial set of evoked potentials performed at the time of hospital admission showed the long-latency components to be preserved. Four days later, cerebral edema developed in the patient and the long-latency evoked potential components were no longer present. The patient died ten days later. The third patient suffered a large right cerebral infarct, and evoked potentials were measured on the third hospital day when the patient was comatose with signs of increased intracranial pressure. His condition deteriorated gradually, and evoked potentials measured on the 18th day showed the long-latency components to be absent. Six days later, the patient died. Thus, the relationship between the presence of long-latency components and survival from coma is affected if the measures are made early in the course of an evolving pathological process. However, if the results of the evoked potentials are considered only in those patients whose conditions had stabilized, the preservation of long-latency evoked potential components does correlate with survival (six of six patients).

When the various auditory evoked potentials were analyzed as to their being normal or abnormal, there was a tendency for those patients with normal potentials to have a greater chance for survival. Four of the eight patients with normal auditory brain-stem potentials survived, whereas only five of the 14 patients with abnormal auditory brain-stem potentials survived. The two patients with normal long-latency potentials survived, whereas only four of the seven patients with abnormal long-latency components survived.

The evoked potential data were analyzed with regard to the cause of coma. In the four patients who survived with an anoxic or metabolic cause of coma, all of the various latency evoked potential components were present. In contrast, in the five patients who survived with a traumatic or vascular cause, there was no particular pattern of evoked potential preservation found: all types of

Table 1.—Survival From Coma and the Pattern of Preserved Auditory Evoked Potentials

	Long and Middle Latency and Brain Stem	Middle Latency and Brain Stem	Brain Stem	None
All causes	6/9*	2/5	1/8	0/3
Anoxia	3/4	0/2	0/5	0/2
Trauma	1/1	2/3	1/1	0/1
Other†	2/4	...	0/2	...

*Number of survivors/number tested.
†Vascular, hepatorenal, hydrocephalus.

Table 2.—Survival From Coma and Neurological Findings*

	Preserved	Absent
Pupillary reflex	7/13†	2/12
Respirations	8/17	1/8
Oculovestibular reflex	6/11	3/14

*Data for motor activity are as follows: normal, 0/2; decorticate or decerebrate, 6/10; and flaccid, 3/13.
†Number of survivors/number tested.

evoked potentials present, two of three patients survived; middle-latency and brain-stem potentials preserved, two of three patients survived; only brain-stem components present, one of three patients survived. Furthermore, the correlation between the absence of long-latency evoked components and survival varied with the cause of coma: in anoxia, their absence was uniformly associated with death (nine patients), whereas their absence in trauma was uninstructive (three of the six patients without long-latency components survived).

There was no correlation between the quality of survival and the presence or absence of the various evoked potentials. Of the nine survivors, two were functioning well, one was moderately disabled, and six were severely disabled or in a chronic vegetative state. While the two patients with a good outcome had long-latency components evident early in their illness, there were four patients with poor outcomes who also had long-latency components preserved.

When the results of the clinical examination were analyzed with regard to the patient's outcome, no relationship could be identified between survival from coma and the presence of pupillary responses, oculovestibular reflexes, preserved spontaneous respirations, or motor behavior (Table 2). The evoked potential results were then compared with the clinical findings from the neurological examination. The presence of both long- and middle-latency potentials was associated with intact pupillary responses (11 of 13 patients, $P < .02$) and oculovestibular reflexes (nine of 11 patients, $P < .1$). Middle-latency potentials in the absence of long-latency components did not correlate with the presence of intact pupillary responses. Finally, there were no substantial correlations between the presence or absence of any of the types of evoked potentials and the occurrence of spontaneous respirations. We were also unable to define a correlation between the degree of EEG abnormality and the patterns of preserved evoked potentials.

COMMENT

The results of this study of patients in coma due to various causes suggest that survival may be correlated with the pattern of preserved auditory evoked potentials. When long-, middle-, and short-latency brain-stem components were all preserved, there was a substantially better chance of survival (six of nine patients) than when only the brain-stem potentials alone were present (one of eight patients). This latter result conflicts with previously reported studies of patients in coma due to head trauma in which the presence of normal auditory brain-stem components did correlate with survival.[6,7] However, when results from the present study are analyzed for only those patients in coma due to head trauma, the relationship between the preservation of an auditory brain-stem potential (five patients) and survival (four patients) also seems to hold. In contrast, in patients in coma due to anoxia, survival could not be related to the definition of brain-stem components (only three of 11 patients with auditory brain-stem components survived). Thus, both the cause of the coma as well as the pattern of auditory evoked potentials appear to influence the probability of survival.

The various auditory evoked potentials are generated at different levels of the nervous system: the short-latency components arise from activation of the auditory pathways within the cochlea and brain stem,[8,9] whereas the middle- and long-latency components depend on the integrity of both primary and secondary auditory cortical regions in the temporal lobe.[10,11] In head trauma, coma may result from functional disturbances localized to the diencephalon, with a good prognosis for recovery, ie, the cerebral concussion syndrome. The auditory brain-stem potentials in these individuals will most likely be normal, whereas the middle- and long-latency components could be affected. However, when trauma is severe, the brain stem can be directly involved with hemorrhage or secondarily affected by uncal herniation. In both of these instances, the prognosis for recovery is poor and the auditory brain-stem potentials will most likely be altered. In contrast, anoxia causes diffuse damage, first in the hippocampus, and next in the remainder of the cerebral cortex and brain stem, making it less likely that any one type of auditory evoked potential will be selectively spared as in trauma.

Somatosensory evoked potential components have also been shown to arise from several different levels of the neuraxis, including peripheral nerve, spinal cord, medial lemniscus, thalamus, and cerebral cortex.[12] De la Torre et al[13] noted that in patients who did not recover from coma, there was both a delay of some of the components as well as a loss of the longest latency events. Hume et al[14] found that the latency difference between the spinal cord (N13) and cerebral (N19) components correlated with recovery from coma only if the measures were made several weeks after the onset of the brain lesion. The present study agrees with that of Hume et al in that the results of auditory evoked potential tests performed early in the course of an evolving process may be misleading. Thus, both the origin of the condition causing the coma as well as the time of evoked potential testing are factors that will affect the predictive value of evoked potentials for survival.

The clinical examination and measures such as the Glascow Coma Scale still provide the most reliable information for prognosis for survival in comatose patients. We do not advocate the routine use of evoked potentials to predict survival in comatose patients. However, in those patients in whom there is uncertainty, the use of evoked potential measures may supplement the clinical examination to increase the accuracy of predicting survival.[6] Certainly, the patients included in the present study had a uniformly poor prognosis for survival

based on their Glascow Coma Scale ratings of five or below. When the patients with preserved long-latency auditory evoked potentials were considered separately, their probability of survival was notably enhanced. In those patients, some aspects of auditory cortical function were preserved, perhaps reflecting a lesser degree of neural involvement when compared with the patients without long-latency evoked potential components.

The pattern of evoked potential preservation was of no value in predicting the quality of survival from coma. This finding might have been anticipated, perhaps, since the auditory potentials studied reflect activity in the primary auditory pathway, structures not particularly involved in cognition, social interaction, or drives and motivations, factors that are relevant for effective social functioning. It may be that the development of techniques to study endogenous or cognitive evoked potentials will provide an opportunity to measure the development of some of the cognitive processes relevant for the quality of survival in patients recovering from coma.

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