Brain Death: Determination with Brain Stem Evoked Potentials and Radionuclide Isotope Studies

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Summary

Thirty-three patients fulfilling the clinical criteria for brain death were tested by Brainstem Auditory Evoked Potentials (BAEP) and Radionuclide Cerebral Angiography and Brain Perfusion Studies. There was a significant correlation between the BAEP and radionuclide study outcomes. All patients with absence of BAEP showed no cerebral perfusion. These findings, added to the clinical findings, resulted in a final diagnosis of brain death in all patients. It is concluded that BAEP and Radionuclide Cerebral Perfusion studies are useful adjuncts for proving that brain death has really occurred.

Keywords: Brain death; brainstem auditory evoked potentials; radionuclide isotope scintigraphy.

Introduction

Traditionally, definition of death has been based on cessation of heartbeat and respiration, and physicians have used the absence of respiratory and cardiac function as the major criteria. However, with the development of respiratory and cardiac resuscitation techniques, respiration is being artifically maintained by mechanical devices, and thus the heart is kept beating but the brain may be completely destroyed. Consequently, the concept of death has changed and brain death is now considered to denote the medical death of the human being. To describe these states between life and death, the term "coma dépassé", a condition beyond deep coma, was coined by Mollaret thirty years ago¹⁶. Today, the concept of brain death is widely accepted as a criterion of death, since cerebral and brain stem functions have irreversibly ceased and cardiac asystole will occur sooner or later^{12, 13, 15, 17, 18, 24, 26}. It is obvious that some isolated groups of cells may still stay alive for a short period of time after the cessation of the brain function shown clinically.

The concept of brain death has given rise to many medical, legal and social problems since its introduction. For all these reasons a need to prove brain death solidly became mandatory in many countries. A number of organizations and groups have formulated sets of criteria for brain death most of which have been based on a combination of the clinical findings of cessation of all brain stem and cerebral functions and various confirmatory tests. Laboratory studies and confirmatory tests are used only as adjuncts to clinical examination or as a means of confirming the irreversibility of the clinical state. Many criteria for determination of brain death have been published by authors from different countries and in all criteria the great importance of clinical neurological findings was stressed^{4, 8, 9, 10, 11, 12}. There have been rapid advances in the diagnostic measures and in the pathophysiological analysis of brain viability in recent years. Therefore, some changes have been made in clinical guidelines and revised criteria and new confirmatory tests have been developed^{1, 7, 11, 13, 17, 18, 19}.

Early recognition and declaration of brain death is very important; because such a patient occupies an intensive care unit bed which will benefit a treatable patient and besides continued treatment of such a patient subjects the family to uncertainty and raises false hopes. In addition, with the declaration of brain death, there arises the possibility of retrieving transplantable organs from the patient^{3, 4, 5, 13, 15, 18}. For these reasons and in order to minimize delay of a definite diagnosis, confirmatory tests should be performed as soon as possible. On the other hand, before declaring brain death, a period of observation is needed to confirm the irreversibility of loss of neurological functions. When the clinical criteria exist, it is repeated after six hours. However, without confirmatory tests and if the diagnosis is uncertain or if confusing secondary problems exist, it is advisable to wait for 12–24 hours after the patient first meets the clinical criteria of brain death. The use of confirmatory tests will make the families understand the finality and shorten the period of observation.

On experimental and clinical grounds, it is asserted that cerebral death has mostly been associated with severe impairment of CBF or intracranial circulatory arrest. But it has to be mentioned that after a period of complete cerebral circulatory arrest some restoration of cerebral perfusion may occur, in spite of the fact that during circulatory arrest the central organ definitely was destroyed. Inadequate blood flow to the brain results in irreversible brain damage within minutes.

A confirmatory test to demonstrate the absence of cerebral blood flow is suggested when an early diagnosis of brain death is considered. Cerebral circulation can be demonstrated in several ways such as conventional or Digital Subtraction Angiography, CT- or Radionuclide Angiography. Complete cessation of brain stem functions is another well known major component of brain death. The brain stem auditory evoked potential (BAEP) recordings are useful to demonstrate if there is no reaction to incoming stimuli in the brain stem nuclei of the auditory pathways^{2, 6, 8, 9, 10, 14, 22, 25}.

Cerebral blood flow studies by radionuclide cerebral angiography (RCA) and cerebral perfusion study by SPECT with 99 mTc-HMPAO and brain stem auditory evoked potentials have been used as the primary confirmatory tests for brain death in the Department of Neurosurgery of Hacettepe University over the last two years. In a 24-month period, we carried out BAEP in 33 patients and radionuclide assessment in 21. We describe here the BAEP and radionuclide patterns found in patients evaluated for possible brain death and correlate the BAEP and radionuclide isotope study findings.

Materials and Methods

- All patients fulfilled the cardinal, basic clinical criteria of brain death: 1-Complete unresponsiveness, 2-Apnoea confirmed by apnoea test, 3-Fixed and dilated pupils, 4-Absence of brain stem reflexes. All appropriate diagnostic and therapeutic procedures were performed for all patients. Attempts were made to maintain blood volume and arterial blood pressure at a satisfactory level and vasopressors were used when indicated. Correction of electrolyte imbalance and administration of steroids were used when necessary. In our study group, criteria for reliable recognition of brain death were not considered to be available in the presence of hypothermia, drug intoxication, endocrine and metabolic disorders and cardiovascular shock, since confirmatory tests can give false positive results in these complicating conditions.

Between October 1987 and September 1989, 33 patients with suspected brain death were admitted to the Intensive Care Unit of the Neurosurgical Department at Hacettepe Medical School. After the diagnosis of brain death was established by neurological examination, RCA and tomographic brain perfusion studies were performed in 21 patients and BAEP was performed in 33 (Table 1). The time from clinical recognition of brain death to imaging ranged from 6 to 24 hours. BAEP was done at the bedside in the intensive care unit and radionuclide studies were done in the Department of Nuclear Medicine which is located across the corridor in our institution.

The purpose of RCA was to image absence of CBF using 99 m-Tc-DTPA. RCA was done within 12 hours of the BAEP assessment. RCA and static brain scintigraphy were performed using 15 mCi 99 m-Tc-DTPA. 120 dynamic images with the matrix size 64×64 were obtained for two minutes in the anterior position, immediately followed with a kidney static (3, 5, 10 and 15 minutes) and anteriorposterior, lateral views of the head. After this study, tomographic brain perfusion imaging was done with approximately 10 mCi 99 m-Tc-HMPAO using SPECT (Single Photon Emission Computerized Tomography, Toshiba 601-GCA). HMPAO was prepared according to the manufacturer's recommendation. Data acquisition started after the iv. injection of 10-15 mCi 99 m-Tc-HMPAO and data was obtained in 60 projections starting as a 64×64 matrix. Transverse, sagittal and coronal images with a slice thickness of 11.2 mm were generated. The imaging criteria for brain death are non-visualization of cerebral arteries and superior sagittal sinus for RCA and absence of uptake for SPECT study.

Auditory brain stem evoked potentials were recorded at the bedside with portable (Medelec ST-10 Er94a) signal generating and computer averaging equipment. Clicks of 100 msec. duration and 75 dB peak equivalent sound pressure level were given mono-aurally at a rate of 10/sec., through shielded earphones (49 P). Brain stem responses were recorded from Ag/AgCl disc electrodes which were placed on the mastoid process and vertex (C2 to A1 or A2). The electrode impedance was less than 5 Kohm. The responses were amplified $1 \times 10,000$ at a band pass of 0.1-3.0 kHz. and averaged over a 10 msec. time base and at least a total of 1024 responses were summated. The responses were integrated by the computer and printed by an x-y plotter.

Results

In a series of 33 patients fulfilling the clinical criteria of brain death, BAEP were studied in 33, radionuclide isotope studies were performed in 21, and both studies were carried out in 20 patients. The ages of the patients ranged from 10 to 63 years. The results are listed in Table 1.

Radionuclide isotope studies were performed in 3 groups; 99 m-Tc-DTPA Kinetic (Radionuclide Cerebral Angiography) in 16 cases, 99 m-Tc-DTPA Static in 18 cases, and 99 m-Tc-HMPAO SPECT (Regional Cerebral Blood Flow) studies in 19 cases. All three radionuclide studies were performed in 14 out of 20 cases.

Tests Performed
Confirmatory
Death
Brain
Had
очм
Patients
in
Findings
Table 1.

-	Age	Sex	Primary Disease	DTPA kinetic	DIFA Static	HMPAO spect uptake	BAEP	Outcome
•	13	Ц	Brain Tumour	None	No Flow	None	No Response	Dead
2	26	Μ	Brain Tumour	10%	No Flow	None	No Response	Dead
ŝ	23	Ъ	SAH	20%	No Flow	None	Suspicious	Dead
4	32	М	Head Trauma	None	No Flow	None	No Response	Dead
5	54	M	Intracer. Haem.	None	No Flow	None	No Response	Dead
6	23	М	Brain Tumour	None	No Flow	None	No Response	Dead
7	19	М	Brain Tumour	None	No Flow	None	No Response	Dead
8	23	М	Brain Tumour	None	No Flow	None	No Response	Dead
6	29	M	Brain Tumour	None	No Flow	None	No Response	Dead
10	41	M	SAH	None	No Flow	None	No Response	Dead
11	44	М	SAH	30%	Sagittal S.	None	No Response	Dead
12	28	Ч	Brain Tumour	20%	Sagittal S.	Cerebellar	Suspicious	Dead
13	33	М	SAH	None	No Flow	None	No Response	Dead
14	38	Μ	Brain Tumour	None	No Flow	None	No Response	Dead
15	53	М	Brain Tumour		No Flow	None	No Response	Dead
16	19	Ц	Head Trauma	1	No Flow	None	No Response	Dead
17	59	М	SAH	I	No Flow	I	No Response	Dead
18	40	ц	Intracer. Haem.	None	No Flow	I	No Response	Dead
19	12	ц	Brain Tumour	1		None	No Response	Dead
20	61	Ĺ	Brain Tumour	10%	I	Irregular	No Response	Dead
21	30	М	SAH	I	I	None	No Response	Dead
22	42	Μ	Head Trauma	I	I	ł	No Response	Dead
23	63	Ν	Head Trauma	I	I	1	No Response	Dead
24	28	Z	Brain Tumour	I	1	1	No Response	Dead
25	14	Ľ.	Head Trauma	I	I	Į	Suspicious	Dead
26	39	M	Brain Tumour	1	I	I	No Response	Dead
27	31	ц	SAH	1	I	1	No Response	Dead
28	34	ĹĿ,	Intracer. Haem.	I	I	ł	Response (+)	Alive
29	10	ليتر	Brain Tumour	-	I	I	No Response	Dead
30	56	М	Brain Tumour	1	I	i	No Response	Dead
31	16	M	Head Trauma	1	1	1	No Response	Dead
32	15	ц	Head Trauma	ł	I	I	No Response	Dead
33	10	ц	Brain Tumour	1	I	1	No Response	Dead

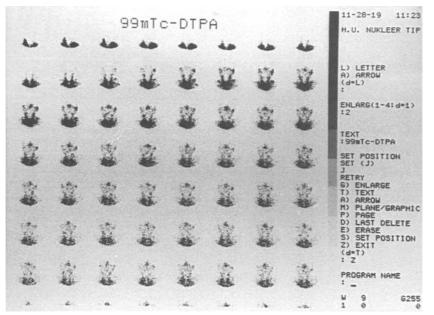
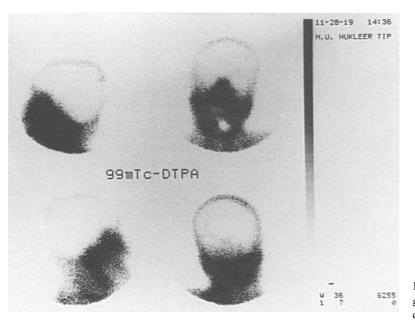
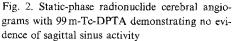


Fig. 1. Kinetic-phase radionuclide cerebral angiograms with 99 m-Tc-DTPA demonstrating cessation of intracerebral blood flow





Eleven out of 16 patients on whom the 99 m-Tc-DTPA Kinetic study was performed had no demonstrable cerebral blood flow. By using a computer programme, the percentages of cerebral circulation were calculated and the following data were obtained; 2 patients had 10%, 2 patients had 20% and another had 30% activity in comparison with the carotid artery.

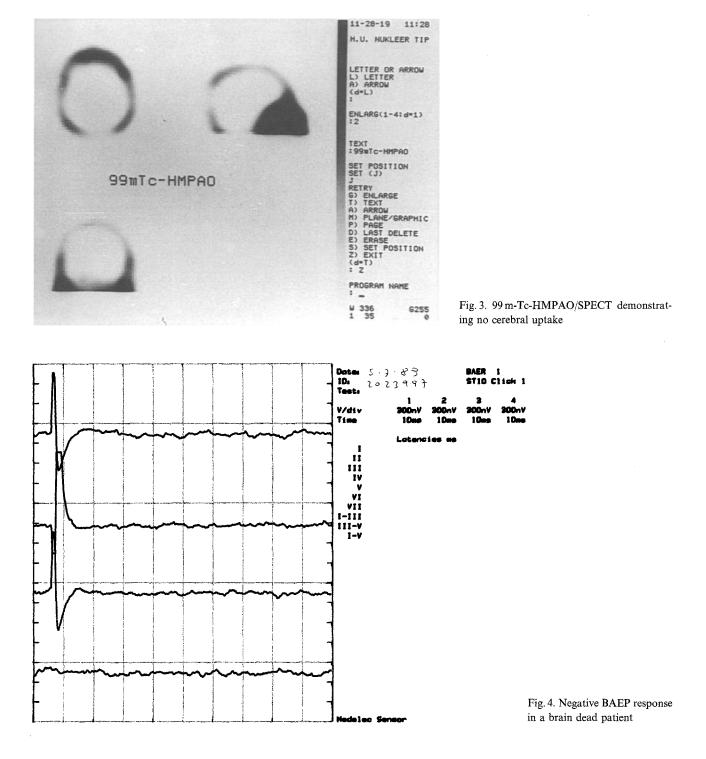
A 99 m-Tc-DTPA Static study was performed in 18 patients and visualization of transverse and sagittal sinuses was obtained in only two cases in this study. The rest showed no cerebral circulation.

99 m-Tc-HMPAO SPECT brain perfusion investi-

gation (Regional Cerebral Blood Flow) was performed in 19 patients. One patient had irregular 99m-Tc-HMPAO uptake, another had cerebellar 99m-Tc-HMPAO uptake. The other 17 patients had no cerebral uptake at all.

The majority of the initial scans in patients showed termination of carotid flow at the skull base and absence of intracranial arterial circulation. When tomographic brain perfusion scanning was performed in this group of patients, it was also found that cortical uptake never appeared on a 99 m-Tc-HMPAO study (Table 1).

BAEP were almost absent in all cases. Only very



suspicious waves could be identified in 3 patients whose serial recordings showed complete disappearance of these waves within 6 hours. Responses could be elicited with normal amplitudes and prolonged I-V intervals in one patient, clinically suspected of brain death, but who recovered within 48 hours and regained brain stem reflexes and spontaneous respiration afterwards (Table 1). The apnoea test had to be discontinued in three minutes in this case, because some drastic changes in the patient's pulse and blood pressure were observed. Respiratory movement of the patient was hardly perceptible, but anyhow, the diagnosis of brain death could not be established in this patient.

Discussion

Discussion about the determination of brain death is still going on and designation of criteria has been an important subject for neurosurgical clinics^{1, 7, 13, 15, 17}. In recent years, criteria based on the results of clinical studies of brain death have been adopted in our department as shown in Table 2.

Brain death can be diagnosed by experienced physicians based on a clinical assessment. However, confirmatory tests may detect possible errors in clinical judgement. Laboratory confirmation is also useful to reassure anxious families that a treatable condition has not been overlooked, and they seem to have less anxiety in accepting the concept of brain death when it is explained in terms of blood flow or other confirmatory tests. Also these tests are useful for providing concrete evidence of irreversibility when there is the possibility of organ transplantation or legal implications and for avoiding unnecessary delays in diagnosing brain death⁴, 5, 13, 15, 18

Cerebral blood flow studies and auditory brain stem responses are clinically useful ancillary tests in the determination of brain death which is mostly associated with intracranial circulatory arrest; so testing of the cerebral circulation seemed to be a direct and rational method. It was shown by Riishede and Ethelberg about 20 years ago that absence of cerebral circulation may be demonstrated angiographically²⁶. A variety of techniques have been used in brain death to demonstrate a critical deficit of cerebral circulation including four vessel cerebral angiography, IV or IA Digital Sub-

All appropriate diagnostic and therapeutic procedures have been performed

Absent corneal, ciliospinal, oculocephalic, pharyngeal and cough reflexes

Radionuclide Cerebral Angiography and Perfusion studies

tracting Angiography, contrast enhanced CT, Doppler Ultrasonography, Radionuclide Cerebral Angiography (RCA) and radionuclide brain perfusion studies. Conventional contrast angiography and most other techniques for determining CBF are fairly invasive methods for routine use in these patients. IV DSA actually can not be considered to be reliable with regard to the proof of cerebral circulatory arrest. Transcranial doppler sonography is a noninvasive and reliable method for the diagnosis of arrest of the cerebral circulation²⁵. RCA and radionuclide brain perfusion imaging seem rather more noninvasive for detecting intracranial blood flow in patients with suspected brain death. They are reasonably safe and can be performed rapidly in the Nuclear Medicine Department. For this reason, it has become the imaging method of choice in our department as in others^{6, 8, 14, 20, 22}.

In our study group, the initial flow and perfusion studies showed no intracranial circulation in almost all the cases. We obtained visualization of sagittal and transverse sinuses in two cases with 99 m-Tc-DTPA Static study. When 99 m-Tc-HMPAO uptake scanning was performed, it was found that cortical uptake never appeared in one of them, while the other patient showed cerebellar uptake. Brill *et al.* reported sagittal sinus visualization in 18 cases with suspected brain death⁶. Schwartz *et al.* suggested that the absence of the arterial phase in the presence of some visualization of a transverse or sagittal sinus was sufficient evidence for brain death. Goodman *et al.* pointed out that confirmation of brain death requires complete nonvisualization of

Brainstem Auditory Evoked Potentials

Table 2. Brain Death Criteria

Children under 6 Hypothermia Drug intoxication

Cardiovascular shock

Known irreparable organic brain lesion.

Endocrine and metabolic disorders

Irreversible deep coma (GCS 3) Apnoea confirmed by apnoea test Bilateral fixed and dilated pupils

Prerequisite

Exclusion

Clinical criteria

Confirmatory tests

123

	Age	Sex	Primary Disease	BAEP
1	2 months	F	Intraventricular Haem.	No Response
2	3.5 years	М	Head Trauma	No Response
3	5 years	F	Guillian Barre	Suspicious
4	6 years	F	Metabolic Disorder	No Response
5	8 months	М	Brain Tumour	No Response

Table 3. BAEP Results of Children with Suspected Brain Death

all intracranial vascular structures and they encountered a delay in diagnosing brain death in over half of their patients while waiting for sequential scans to show disappearance of uptake in sinuses⁸. In spite of this protocol, in Goodman's series, once unequivocal absence of the cerebral arterial circulation was demonstrated by isotope angiography, it was never seen to return on sequential scans. Also, we have never seen a return of cerebral circulation in patients whose sagittal sinuses only were visualized. However we believe that, if the sinuses are visualized in isotope uptake with 99 m-Tc-DTPA, a BAEP study should be performed to confirm brain death.

The brain stem evoked potential response recording is a clinically useful ancillary test in the determination of brain death. Unlike the EEG, BAEP measurement is not invalidated by acute medical therapy such as chemical paralyzing agents and high dose barbiturates. BAEP may provide more reliable information on brain stem function than EEG and is accepted by many clinicians as the primary laboratory test for confirming brain death9, 10. Brain stem auditory evoked potentials are objective measurements of the functions of the cochlear and auditory pathways in the brain stem. The metabolic and physiological immutability of BAEP provides a safety margin for use of the test in comatose patients. For example, in a case of barbiturate overdose sufficient to produce the clinical appearance of brain death and isoelectric EEG, BAEP gives a normal response. Therefore this test can be an indicator of preserved brain stem functions in difficult situations. And brain death should only be diagnosed if it demonstrates that no reaction to incoming stimuli is occurring in brain stem nuclei, except for the first (cochlear) wave⁹, 10, 23

In our study, three patients showed a suspicious BAEP response. In one of these the result of the radioisotope study was accepted as suspicious brain death and in another, 20% activity was found in the DTPA kinetic study. Radio-isotope study of the third patient could not be performed. In twelve patients only BAEP was studied and no radionuclide studies were performed. One patient who showed a normal BAEP response in this group, progressed well clinically and another patient who was found to have a suspicious response, developed a negative BAEP response when the test was repeated 6 hours later. In two cases we were unable to detect BAEP due to excessive ambient noise or EMG contamination. Beside this, there are some limitations of BAEP in the study of patients with dead brains; if none of the BAEP components can be demonstrated, there is doubt about the side at which the auditory function is compromised. In cases of head injury, for instance, cochlear or auditory nerve damage secondary to fracture of the temporal bone, injury to the middle ear or collection of blood in the external auditory canal may cause or contribute to the nondetectability of BAEP. Because of this limitation, the diagnosis of brain death was demonstrated by radionuclide angiography and brain perfusion study. In our study, all patients except one who had a good BAEP response, died within 48 hours of the BAEP test.

BAEP outcome is highly correlated with the results of nuclear CBF studies in the determination of brain death. In 19 out of 21 cases presenting the criteria of brain death, radionuclide studies demonstrated cessation of cerebral circulation and in 18 cases, both BAEP and radionuclide studies demonstrated an absence of auditory brain stem response and CBF. These findings, resulted in a final diagnosis of brain death in these patients. The ventilator was subsequently withdrawn in three patients after removal of the liver and kidneys for transplantation with the permission of the families. The majority of those who remained on the ventilator succumbed to circulatory arrest within 48 hours without any clinical evidence of brain activity. Only one young girl remained on the ventilator for 6 days.

A BAEP study was performed in 5 patients who were between two months and six years old. The results are shown in Table 3. Since brain death criteria in children have not yet been definitively established, the lack of specific and universally accepted diagnostic criteria is a serious problem. Accordingly we believe that the criteria for determining brain death in adults should not be adapted to children. Much experience is needed before establishing criteria in the paediatric age groups, and thus we have excluded these patients from our study because the number of cases is considerably less than in the adult group. Brain death in anencephalic infants and their being transplantation donors is an issue currently been discussed. We have not made any approach to this problem in our paper since this discussion carries different medical, ethic and legal dimensions.

Several aspects of brain death are still subject to discussion. While in a small number of countries brain death is announced only on the basis of clinical criteria, in the majority of countries different confirmatory tests are employed. It is extremely important to educate society without injuring its traditional beliefs and understanding of death especially in developing countries such as ours. Because increasing demand for transplantable organs will follow the announcement of brain death, determination should depend upon solid clinical criteria and confirmatory tests. We believe that in order to prevent any questionable outcome, for medical, ethical, legal and religious aspects, at least two confirmatory tests should be used and results obtained should be in complete accord. It is our opinion that because of its simplicity, portability and low cost, BAEP should be the first study when brain death is suspected and radionuclide cerebral angiography and radionuclide brain perfusion studies should be performed as the definite proof, especially when organ transplantation is considered.

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