Determining Brain Death: Back to the Basics

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ABSTRACT

The subject of brain death usually becomes clinically relevant during a tremendously stressful time. For most practitioners, the need to make a diagnosis of brain death occurs infrequently. Since the introduction of the concept of brain death, the criteria have been refined to their current state. The historical background and the current standards and guidelines used to diagnose brain death will be reviewed. Potential future changes in brain death criteria when contemplating organ donation in the critically ill patient will be discussed.

KEYWORDS: Brain death, confirmatory tests, apnea test, organ donation

Defining death has evolved as medical knowledge and technology have advanced. It was the development of the artificial ventilator more than 40 years ago that prompted the discussion and reassessment of the concept of what actually constitutes death. Prior to the wide availability of reliable ventilators, death usually meant cessation of cardiac function. The initial attempts at defining the criteria of what constituted death in the ventilator age began in 1968 with the “Harvard criteria,”¹ which based the concept of brain death on neurologic criteria.

The Harvard committee on the development of the new criteria of “irreversible coma” as brain death consisted of members from the Medical, Divinity, Public Health, Graduate, and Law Schools. Physician members included an anesthesiologist, a neurosurgeon, and a neurologist. The final proposed criteria were not derived from evidence-based medicine principles but from the prior experiences of the committee members. The product was published in JAMA in August 1968 and included comments from Pope Pius XII. The final criteria put forward were succinct and required that the patient demonstrate unreceptivity and unresponsivity, no movements or breathing, no reflexes, and a “Flat EEG.” The examination and electroencephalogram (EEG) were required to be repeated 24 hours or later in the absence of hypothermia and central nervous system (CNS) depressants.

After dissemination of the Harvard criteria, various states and countries proposed and enacted their own additional criteria to meet their specific location’s definition for brain death. Further studies and a United States presidential commission on the subject were reported in the 1970s and 1980s. Continuous reevaluation of the criteria in the 1990s resulted in the American Academy of Neurology (AAN) establishing guidelines for brain death determination (Table 1).

CASE 1

An 18-year-old male fell from a pick-up truck driven by his father while traveling ~45 miles per hour and had a severe closed head injury. While on the way to the hospital, he has several seizures without regaining consciousness. The initial computed tomography (CT) scan shows bilateral subdural hematomas and intracerebral hemorrhages. The subdural hematomas required drainage with bilateral craniotomies. The patient regained consciousness, but several days postoperatively massive brain swelling began and the patient lost all brain-stem reflexes and remained ventilator dependent. As the situation progressed, brain tissue actually oozed from

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the craniotomy suture lines. The family and guilt-ridden father refused to believe that the patient could be dead with the "heart still beating" and demanded an EEG be completed to be sure he was really brain dead. When informed that an EEG would be technically difficult due to the prior craniotomies and scalp swelling, they asked for a second opinion.

Case 1 Discussion
This case highlights several issues about the topic of brain death. Despite the fact that the medical community and medical practitioners have refined the concept of brain death over the past 50 years, some practitioners and lay people still believe that an EEG is still needed to confirm brain death. Recalling that the EEG once was required in the original Harvard committee's recommendations to confirm brain death, people still discuss the EEG as being "flat line."

Confirmatory Tests for Brain Death
Confirmatory tests for brain death are the subject of much study and reporting. In general, the confirmation of brain death starts and usually ends with the appropriate neurologic and physical exams. On occasion, when portions of the exam are determined to be unreliable, a confirmatory test may be used to assist in making the definitive diagnosis.

Physical Examination
Certain conditions are required before the diagnosis of brain death may be made and include the following: (1) an irreversible acute definitive significant event occurs involving the cerebral hemispheres and/or brain stem; (2) no significant comorbid medical conditions may be present that could confound the situation (electrolyte, endocrine, etc., disturbances); (3) the presence of no intoxicating drugs, neuromuscular blocking agents, or poisons; and (4) no hypothermia (core temperature > 32°C).2

Once these conditions are met, the physical exam should include the testing of multiple levels of the brain and brain stem. Testing for the cerebral cortex in the comatose patient is commonly completed by noxious and auditory stimulation. Common techniques include the application of painful pressure to nail beds, supraorbital nerves, or temporal mandibular joint. Nasal tickle (cotton swab inserted in the nares) is a noxious stimulus that does not involve pain. Auditory stimulus commonly includes voice and loud noises near the patient. No visible response to noxious stimulation or auditory stimulation is needed to diagnose brain death.

Evaluating brain-stem function in the comatose patient is completed by reflex testing of the midbrain, pons, and medulla. Pupillary response to direct stimulation by intense light will remain intact even if the patient is on sedative systemic medications at usual doses. Direct use of ophthalmic drugs or eye trauma may impair this important response. Evaluation of eye movements is done by testing the oculocephalic reflexes. Rapid turning of the head 90 degrees on each side is the initial technique used, looking for the absence of eye movement in response to the change in head position. Perhaps more sensitive than head turning is caloric testing using ice water. Highlights of this technique include keeping the patient's head at 30 degrees from the horizontal and irrigating the external auditory canal with a large amount of ice water (50 mL). The expected response is a slow movement of the eyes toward the side in which the ice water is inserted and may take as long as 60 seconds before a movement is seen. Several minutes must elapse between testing each side allowing the temperature on the side just tested to normalize so as not to inhibit any reaction on the side about to be tested. Corneal reflexes are tested by direct stimulation to the cornea using a stimulus that will not injure the eye, such as a cotton tip applicator. An intact response is noted when the patient attempts to blink when the stimulus is applied and when present is not consistent with brain death. Although often difficult to assess when a patient is intubated, the jaw jerk reflex should also be absent in brain death. A cough reflex is tested by suctioning the patient for several seconds with a suction catheter inserted in the endotracheal tube. Evaluation of the gag reflex is difficult when the patient is orally intubated.

Testing for apnea deserves special consideration in that its presence can be somewhat objectively tested with the well-described apnea testing protocol.3–6 Features of the protocol include applying 100% oxygen to the trachea before the respirator is disconnected followed by the serial measurements of the patients PaCO2. The lack of visible respiratory effort after reaching a target PaCO2 of 60 mm Hg or rise of 20 mm Hg is considered a positive test. Concern over the theoretical potential of the test causing hypotension and hypoxemia in the organs of patients being considered for transplant.

Table 1  AAN Guidelines for the Determination of Brain Death

| Apnea |
| Absent brain-stem reflexes |
| Absent motor responses |
| Absence of confounding factors* |
| Demonstration of coma |
| Evidence for cause of coma |
| 6-hour repeat evaluation advised |

Confirmatory tests required when specific clinical exam components are not reliable1

*Hypothermia, drugs, and electrolyte and/or endocrine disturbances.

1See “Confirmatory Tests for Brain Death” section.
has been expressed but has not been verified in clinical practice. Apnea may be confirmed by visual observation or with EMG leads testing appropriate respiratory muscles. Hypotension is recognized as a common complication of the apnea test and is usually avoided by adequate pretesting oxygenation, and the continued application of oxygen after removal from the ventilator. Vasopressor support may be needed to complete the test. If the apnea test is not able to be performed adequately, other confirmatory tests should be considered, especially if the patient is being considered for organ harvesting.

In our case, the request for confirmatory EEG testing made by the family of the patient will likely add nothing to the situation and has the potential to confuse the situation. A so-called flat or isoelectric EEG is historically associated with brain death. The intensive care unit (ICU) is a technically hostile environment for EEG testing and is prone to multiple sources of artifact including ventilator, 60 Hz, electric bed, electrocardiograph (ECG), and other extraneous artifacts (Fig. 1). Minimal technical guidelines for performing an EEG for brain death determination are well established and are outlined in Table 2. The sensitivity and specificity of EEG in this situation has been reported to be ~90%.12

Ancillary Confirmative Tests

Other tests looking at cerebral blood flow are commonly used to confirm brain death and include cerebral angiogram, single photon emission computed tomography (SPECT) scanning, transcranial Doppler ultrasound testing (TCD), and magnetic resonance angiography (MRA). Formal cerebral angiogram, TCD, SPECT scanning, and MRA are all used to demonstrate the lack of cerebral blood flow, thus confirming brain death. These tests confirm no cerebral blood flow by direct visualization or indirectly with a nuclear “tracer.” TCD may be done at the bedside, but MRA, SPECT scan, and angiogram testing must generally be done outside the ICU. Moving a critically ill patient on a ventilator presents a logistical challenge, especially if the patient is medically unstable. A recent study looking at TCD versus cerebral angiogram showed that TCD is as effective as angiography for determining brain death. A SPECT scan helps confirm the diagnosis when it shows no uptake in the cerebral hemispheres, reflecting no blood flow state. Cerebral angiogram and MRA visualize the lack of blood flow within the vessels that supply the brain. TCD is a measure of flow within blood vessels in the supratentorial region and may not be an accurate confirmatory test for those patients afflicted with a brain-stem lesion. TCD and tests evaluating cerebral blood flow may be misleading in cases of severe brain-stem dysfunction by showing cerebral blood flow despite meeting accepted physical exam criteria for brain death. TCD has a relatively high sensitivity of ~95% and specificity of 100% when used in the proper clinical situations.

Evoked potentials may also assist the practitioner in assessing brain death. Brain-stem function is reflected in the electrical activity of the brain-stem auditory-evoked response (BAER). The auditory nerve is stimulated using an auditory stimulus composed of a click stimulus introduced at the bedside though earpieces. Somatosensory-evoked potentials (SSEPs) are recorded along the spine along with far-field recordings from the parasagittal scalp region contralateral to a peripheral nerve that has been stimulated either in the upper or lower limb. Bilateral absence of the N20 component of the SSEP with median nerve stimulation recorded on days 1 to 3 after cardiopulmonary resuscitation is predictive of a poor outcome, but there are no recommendations for the use of routine evoked potentials in determining brain death.20–24

In the previously discussed case 1, a family meeting was held with the ICU staff and neurology. During the meeting, the principles regarding ancillary testing as outlined above, and specifically EEG testing, were discussed. The family eventually understood that the EEG was not necessary to confirm brain death. Due to religious reasons, organ donation was not an option. An apnea test was completed confirming brain death, and the ventilator support was discontinued.

CASE 2

An 85-year-old man with uncontrolled hypertension was admitted to the hospital in coma with a massive intracerebral hemorrhage. He has several hundred thousand dollars in the bank and lives with his wife in his own home. Brain death is diagnosed based on the physical exam. Other family members hear of the unfortunate occurrence. His estranged son who has not seen the father for 30 years flies in from out of state and demands that the hospital staff do anything and everything to “keep his father alive, no matter what the cost.” The son felt that as his heart is still beating, he is still “alive.” The patient had no living will, and the patient’s wife is felt to be competent. The son threatened to bring legal action against the hospital and attending staff if the ventilator is discontinued. Despite the fact that the concept of brain death has been discussed and reviewed for more than 4 decades, confusion still exists about the role of the physician in the brain death process.25 Some health care providers believe that legal counsel is required prior to stopping the supportive therapy in end-of-life situations. Misunderstanding and trepidation exist about the actual management of the discontinuation of therapy at the end of life. Being threatened with legal action adds to the tension in these already difficult situations. Unwanted continued supportive care is a possible
Figure 1  (A) EEG with very low amplitude activity or artifact with the patient meeting clinical criteria for brain death. (B) No EEG activity as the ventilator is discontinued, low-amplitude EMG, and ECG artifact is noted.
consequence if health care providers are unfamiliar with these end-of-life issues.26–28

Once the diagnosis of brain death is made, medical decisions about removing organs or discontinuing supportive therapy usually fall to a specific surrogate. In general, if there is no appointed legal guardian, a specific family member is enlisted to help in the decision-making process, acting as an advocate for the patient. Once a surrogate is identified, it is expected that they will act in accordance with previously expressed wishes of the patient in question (if known). If no wishes were ever expressed previously by the patient, the surrogate should take into account the patient’s religious and cultural background in making end-of-life decisions and withdrawing care.29,30 If the decision is left to next of kin, controversy and conflict will arise among family members called upon to make these difficult decisions. When disagreement occurs among family members about how to proceed, social services and religious authorities familiar with the process may be helpful in the initial attempts at resolution of disagreement between family members or between the family and the hospital. Should these initial attempts at conflict resolution persist, an ethics consultation, hospital legal consultation, or even a court order may be required. Every state in the United States has case law or specific statutes addressing and allowing for the determination of death based on neurologic criteria.31 Many countries address the issue of what constitutes brain death, as defined by a wide variety of requirements and confirmatory tests.32

Fortunately in this case, the son’s feelings of guilt for being out of his father’s life were assuaged during a family meeting with the attending physicians, a pastor, nursing staff, and social worker. During the meeting, the medical facts of the case, the concept of brain death, and an explanation of who ultimately had the legal authority to withdraw care were explained to the son. Finally understanding the situation, the son was supportive of his mother’s decision to withdraw care and allowed his father to be withdrawn from support. The team approach displayed at the family meeting reassured the son that the decision to terminate supportive care was appropriate.

**CASE 3**

J.J. is a 23-year-old motorcycle stunt rider with a copyrighted name and multimillion-dollar business, who fell off of his motorcycle in his front driveway after slipping on some oil. He was not wearing a helmet, struck his head, and lay down with a headache. Later he was found in bed unconscious and taken to the hospital where an epidural hematoma was discovered and evacuated. Suffering massive brain swelling, J.J. remained comatose postoperatively. The patient’s manager wanted to “spare no expense” to keep J.J. alive. Unfortunately, the patient did poorly and after several days he lost all brain-stem function and was declared brain dead. The manager wanted to continue supportive care despite the diagnosis. His wife was unsure about how to proceed.

The diagnosis of brain death may initiate many other events in the lives of the survivors. Important events after one dies include the beginning of the grieving process and transfer of property. Communication of a definitive, timely, and accurate diagnosis of brain death allows for the grieving process to begin. In the age of rising health care costs, continuing supportive futile care in the brain dead individual contributes to both societal and individual monetary burdens, as do unnecessary so-called confirmatory tests. In addition, when the patient dies, pensions and governmental entitlements may be altered and life insurance payouts are triggered.

Health care providers rightfully focus on clinical questions of diagnosis and prognosis of patients in coma or who are brain dead. When the patient dies, a will often specifies how the deceased person’s property is transferred to survivors or others. Although consideration of the patient’s will and transfer of property rarely enter into decisions about stopping treatment, it may at times explain the actions of survivors. The expressed wishes of the brain dead patient as spelled out in the living will must be respected and performed if at all possible.

Discussions about organ donation and transplant naturally are addressed in these situations. The discussion of potential organ donation should be considered early on in the process, especially if the clinical situation appears to be deteriorating. Organ donation was first approved in the United States in the late 1960s.33 The Uniform Anatomical Gift Act defined who could give consent for organ donation, how the organs could be used, and what type of facility could receive the donated organs. In the United States, the United Network for Organ Sharing (UNOS) has been the organization responsible for oversight and regulations governing procurement and distribution of the donated organs (www.unos.org). All hospitals that receive federal monies must follow specific guidelines and policies and pass a certification process by UNOS. The number of people on the waiting list for organs has far exceeded the

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**Table 2** Minimal Technical Guidelines for Performing an EEG for Brain Death Determination

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
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<tbody>
<tr>
<td>Minimum of 10 electrodes</td>
<td></td>
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<tr>
<td>Qualified technologist performing EEG</td>
<td></td>
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<tr>
<td>Long interelectrode distances</td>
<td></td>
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<tr>
<td>Long time constants</td>
<td></td>
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<tr>
<td>Minimum of 30 minutes recording time</td>
<td></td>
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<tr>
<td>No activity greater than 2 μV</td>
<td></td>
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<tr>
<td>No hypothermia</td>
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<tr>
<td>No sedating drugs</td>
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<tr>
<td>Testing of continuity of the recording system</td>
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number of organs available for transplant.\textsuperscript{34} The discussion about organ donation is a natural consequence of managing the nearly brain dead patient and requires a thoughtful and caring approach. Studies have shown that separating the discussion of brain death from the organ donation request improves the donation rate considerably.\textsuperscript{35–37}

The patient’s wife was informed about the diagnosis of brain death, and she was concerned as J.J.’s manager had advised her to “keep everything going.” The patient’s wife discovered a living will prepared several months ago that directed no life support should be continued if there was no hope of recovery. It was explained to her that J.J.’s manager had no say in the matter of continuing care. Thirty minutes after the patient was pronounced brain dead, an organ procurement specialist inquired about organ donation. His wife followed J.J.’s wishes according to the living will, and life support was discontinued. In conjunction with stopping therapy, J.J. donated his heart, liver, lungs, and kidneys. The copyright of J.J.’s name and image and business ownership was transferred to J.J.’s wife.

**FUTURE DIRECTIONS IN BRAIN DEATH DETERMINATION**

Advances in transplant medicine and an increasing need for transplantable organs has brought death determination full circle for potential organ donors. Circulatory death was the accepted norm before the advent of the ventilator and subsequent development of the concept of brain death. The concept of donation after circulatory death (DCD) has been recently introduced nationally and became effective in January 2007.\textsuperscript{38} The concept requires the mandatory implementation of organ donation after DCD. DCD involves those patients who do not meet the current definition of brain death before the ventilator is removed. The basic tenets of DCD allow for organ procurement after 5 minutes of unresponsiveness, pulselessness, and apnea. Questions have been raised about the DCD process in patients not fulfilling neurologic brain death criteria and subsequent organ procurement.\textsuperscript{39}

**CONCLUSION**

Outside of major medical institutions, brain death issues occur less frequently. The concept of brain death is firmly established in the culture of the many nations. Variability of how the diagnosis is made does exist among the various countries that recognize the entity. Therefore, one needs to be familiar with the key issues of making the diagnosis of brain death. The American Academy of Neurology has recently reaffirmed, as of January 2007, the current practice parameter on determining brain death (www.aan.com/professionals/practice/guidelines/pda/brain_death_adults.pdf). The accurate and timely determination of brain death has implications other than just stopping supportive care. The clinician involved in these situations should be aware of the major implications of withdrawing care in the brain dead individual and the apparent proposed changes in the approach to the potential organ donor in the ICU that are on the horizon.

**REFERENCES**

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