Review Articles

Current Concepts

The Diagnosis of Brain Death

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PHYSICIANS, health care workers, members of the clergy, and laypeople throughout the world have accepted fully that a person is dead when his or her brain is dead. In the United States, the principle that death can be diagnosed by neurologic criteria (designated as brain death) is the basis of the Uniform Determination of Death Act,[1] although the law does not define any of the specifics of the clinical diagnosis. There is a clear difference between severe brain damage and brain death. The physician must understand this difference, because brain death means that life support is useless, and brain death is the principal requisite for the donation of organs for transplantation. In adults, the chief causes of brain death are traumatic brain injury and subarachnoid hemorrhage.[2] In children, abuse is a more common cause than motor vehicle accidents or asphyxia.[3] The ethical, religious, and philosophical considerations regarding the definition of death have been addressed in a recent monograph.[4] This review focuses on the clinical determination of brain death in adults and children, including the potential confounding factors, and provides an overview of valid confirmatory tests.

EVOLUTION OF THE CRITERIA FOR BRAIN DEATH

The widespread use of mechanical ventilators that prevent respiratory arrest has transformed the course of terminal neurologic disorders. Vital functions can now be maintained artificially after the brain has ceased to function.

In 1959, Mollaret and Goulon[5] introduced the term *coma dépassé* (irreversible coma) in describing 23 comatose patients who had lost consciousness, brain-stem reflexes, and respiration and whose electroencephalograms were flat. In 1968, an ad hoc committee at Harvard Medical School reexamined the definition of brain death and defined irreversible coma, or brain death, as unresponsiveness and lack of receptivity, the absence of movement and breathing, the absence of brain-stem reflexes, and coma whose cause has been identified.[6] In 1971, Mohandas and Chou[7] described damage to the brain stem as a critical component of severe brain damage. The Conference of Medical Royal Colleges and their Faculties in the United Kingdom[8] published a statement on the diagnosis of brain death in 1976 in which brain death was defined as complete, irreversible loss of brain-stem function. This statement provided guidelines that included a refinement of apnea testing and pointed to the brain stem as the center of brain function: without it, no life exists. In 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published its guidelines.[9] This document recommended the use of confirmatory tests to reduce the duration of the requisite period of observation but recommended a period of 24 hours for patients with anoxic damage, and it made the ruling out of shock a requirement for a determination of brain death. More recently, the American Academy of Neurology conducted an evidence-based review and suggested practice measures. This report specifically addressed the tools of clinical examination and the validity of confirmatory tests and provided a practical description of apnea testing.[10]

THE CLINICAL EXAMINATION

The clinical neurologic examination remains the standard for the determination of brain death and has been adopted by most countries. The clinical examination of patients who are presumed to be brain dead must be performed with precision.[10,11] The declaration of brain death requires not only a series of careful neurologic tests but also the establishment of the cause of coma, the ascertainment of irreversibility, the resolution of any misleading clinical neurologic signs, the recognition of possible confounding factors, the interpretation of the findings on neuroimaging, and the performance of any confirmatory laboratory tests that are deemed necessary. One may argue that the decision should be made by a neurologist or a neurosurgeon, but the necessary degree of expertise is not readily available in many smaller hospitals. No data suggest that a second assessment by a different physician reduces error or reduces the possibility of negligence. Nevertheless, there are major differences among countries in the requirements for the number of observers, the specialty of the assessing physician, the duration of observation, and the use of confirmatory tests.[12]

Neurologic examination to determine whether a

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patient is brain dead can proceed only if the following prerequisites are met: the ruling out of complicated medical conditions that may confound the clinical assessment, particularly severe electrolyte, acid–base, or endocrine disturbances; the absence of severe hypothermia, defined as a core temperature of 32°C or lower; hypotension; and the absence of evidence of drug intoxication, poisoning, or neuromuscular blocking agents.

Interpretation of the computed tomographic (CT) scan is essential for determining the cause of brain death. Usually, CT scanning documents a mass with brain herniation, multiple hemispheric lesions with edema, or edema alone. However, such a finding on the CT scan does not obviate the need for a careful search for confounders. Conversely, the CT scan can be normal in the early period after cardiorespiratory arrest and in patients with fulminant meningitis or encephalitis. Examination of the cerebrospinal fluid should reveal diagnostic findings in circumstances of infection of the central nervous system.

A complete clinical neurologic examination includes documentation of coma, the absence of brain-stem reflexes, and apnea (Table 1). The examination of brain-stem reflexes (Fig. 1) requires the measurement of reflex pathways in the mesencephalon, pons, and medulla oblongata. As brain death occurs, patients lose their reflexes in a rostral-to-caudal direction, and the medulla oblongata is the last part of the brain to cease to function. Several hours may be required for the destruction of the brain stem to be complete, and during that period, there may still be medullary function.[14] In the unusual circumstances of persistent functioning of the medulla oblongata, there is normal blood pressure, a cough response after tracheal suctioning, and tachycardia after the administration of 1 mg of atropine.

The depth of coma is assessed by documentation of the presence or absence of motor responses to a standardized painful stimulus, such as pressing on the supraorbital nerve, temporomandibular joint, or nail bed of a finger. The examination should then proceed with the assessment of the presence or absence of brain-stem reflexes. If brain-stem reflexes are absent, the examination should document round or oval pupils in midposition with respect to dilatation (4 to 6 mm in diameter) with no response to bright light. No oculocephalic movements should be elicited by rapid turning of the head; however, it may be not only difficult to interpret the results of this test, but also problematic when there is a concomitant spinal injury. The absence of provoked eye movements must be confirmed by testing with cold caloric stimulation; the tympanum should be irrigated with ice water after the head has been tilted 30 degrees. There should be no tonic deviation toward the cold stimulus. The presence of clotted blood or cerumen in the ear canals may diminish the response in a person who is not brain dead. The physician should test the corneal reflex by touching the edge of the cornea with a swab to produce an adequate stimulus. The cough response can best be assessed with bronchial suctioning; moving the endotracheal tube back and forth may not be an adequate stimulus.

After the absence of brain-stem reflexes has been documented, apnea must be formally tested. Apneic diffusion oxygenation is the procedure that is used most commonly to maintain oxygenation during apnea testing (Fig. 1).[15,16] The threshold of maximal stimulation of the respiratory centers in the medulla oblongata (which may be malfunctioning because of damage) has been arbitrarily set in the United States at a partial pressure of arterial carbon dioxide of 60 mm Hg or a value that is 20 mm Hg higher than the normal base-line value. Preoxygenation eliminates the stores of respiratory nitrogen and accelerates the transport of oxygen through an oxygen catheter in the trachea. The mechanical ventilator must be disconnected in order to obtain an appropriate assessment of breathing, because the ventilator's sensors may give false readings.[17] The increase in the partial pressure of carbon dioxide is biphasic and occurs at a rate of approximately 3 mm Hg per minute. This method is simple and usually free of complications, provided that adequate precautions are taken. If complications such as hypotension or cardiac arrhythmia occur, they may be due to a failure to provide an adequate source of oxygen or to a lack of preoxygenation.[18] Very few data

Table 1. Clinical Criteria for Brain Death in Adults and Children.

Coma
Absence of motor responses
Absence of pupillary responses to light and pupils at midposition with respect to dilatation (4–6 mm)
Absence of corneal reflexes
Absence of caloric responses
Absence of gag reflex
Absence of coughing in response to tracheal suctioning
Absence of sucking and rooting reflexes
Absence of respiratory drive at a $PaCO_2$ that is 60 mm Hg or 20 mm Hg above normal base-line values*
Interval between two evaluations, according to patient's age
Term to 2 mo old, 48 hr
>2 mo to 1 yr old, 24 hr
>1 yr to <18 yr old, 12 hr
≥18 yr old, interval optional
Confirmatory tests†
Term to 2 mo old, 2 confirmatory tests
>2 mo to 1 yr old, 1 confirmatory test
>1 yr to <18 yr old, optional
≥18 yr old, optional

*$PaCO_2$ denotes the partial pressure of arterial carbon dioxide.

†See Table 2 for descriptions of the available confirmatory tests. Tests may be required by law outside the United States.

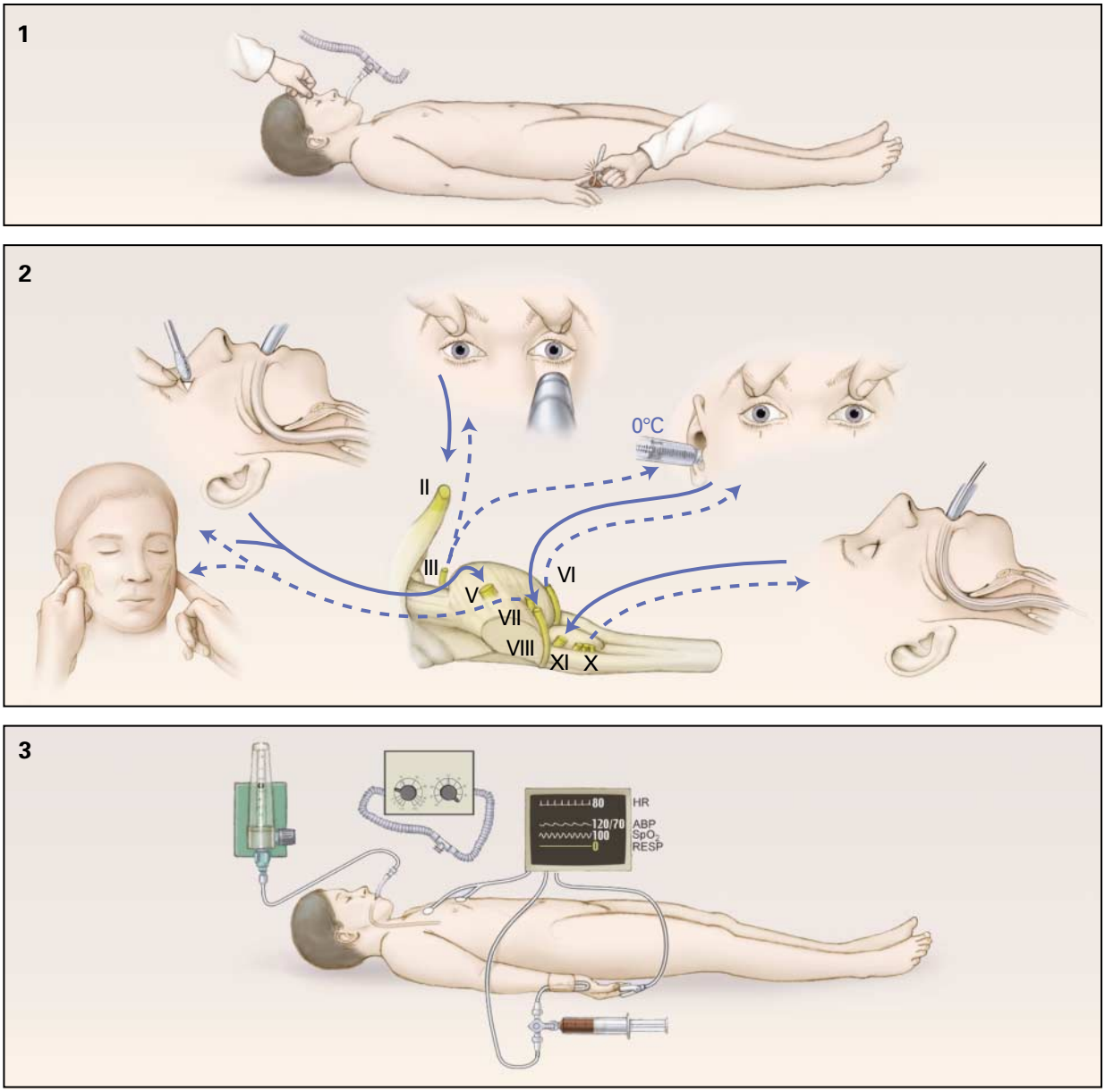


Figure 1. The Steps in a Clinical Examination to Assess Brain Death.

In step 1, the physician determines that there is no motor response and the eyes do not open when a painful stimulus is applied to the supraorbital nerve or nail bed. In step 2, a clinical assessment of brain-stem reflexes is undertaken. The tested cranial nerves are indicated by Roman numerals; the solid arrows represent afferent limbs, and the broken arrows efferent limbs. Depicted are the absence of grimacing or eye opening with deep pressure on both condyles at the level of the temporomandibular joint (afferent nerve V and efferent nerve VII), the absent corneal reflex elicited by touching the edge of the cornea (V and VII), the absent light reflex (II and III), the absent oculovestibular response toward the side of the cold stimulus provided by ice water (pen marks at the level of the pupils can be used as reference) (VIII and III and VI), and the absent cough reflex elicited through the introduction of a suction catheter deep in the trachea (IX and X). In step 3, the apnea test is performed; the disconnection of the ventilator and the use of apneic diffusion oxygenation require precautionary measures. The core temperature should be 36.5°C or higher, the systolic blood pressure should be 90 mm Hg or higher, and the fluid balance should be positive for six hours. After preoxygenation (the fraction of inspired oxygen should be 1.0 for 10 minutes), the ventilation rate should be decreased. The ventilator should be disconnected if the partial pressure of arterial oxygen reaches 200 mm Hg or higher and if the partial pressure of arterial carbon dioxide reaches 40 mm Hg or higher. The oxygen catheter should be at the carina (delivering oxygen at a rate of 6 liters per minute). The physician should observe the chest and the abdominal wall for respiration for 8 to 10 minutes and should monitor the patient for changes in vital functions. If there is a partial pressure of arterial carbon dioxide of 60 mm Hg or higher or an increase of more than 20 mm Hg from the normal base-line value, apnea is confirmed. ABP denotes arterial blood pressure, HR heart rate, RESP respirations, and SpO_2 oxygen saturation measured by pulse oximetry. Adapted from Wijdicks[13] and reproduced with the permission of the Mayo Foundation.

are available on patients who resume breathing despite the loss of all other brain-stem reflexes, but if breathing does occur, it does so early during the test and typically at a partial pressure of arterial carbon dioxide of about 40 mm Hg.[15] No recent audits of the competence of physicians in determining brain death have been published, but apnea testing has often been conducted without adequate precautions.[18]

The clinical examination to determine brain death in children follows the same principles as that in adults (Table 1).[3] However, many children have hypothermia when they become comatose after a severe brain injury. Several of the cranial-nerve responses are not fully developed in preterm and full-term neonates, and it is difficult to perform a neurologic assessment in an infant who is in an incubator. Because of the limitations on the clinical examination of neonates, an observation period of 48 hours is recommended, as well as a confirmatory test, such as electroencephalography or a study of cerebral blood flow.[19]

The most controversial issue related to the determination of brain death is the occurrence of clinical signs that suggest some retention of brain function.[20-23] Even in the absence of motor responses, spontaneous body movements may be observed during the apnea test, while the body is being prepared for transport, at the time of an abdominal incision for the retrieval of organs, or in synchrony with the respirations produced by the mechanical ventilator.[19,22] These body movements are generated by the spine, and the evidence of brain death in such cases comes from a consistent clinical documentation of brain death and confirmation by isoelectric electroencephalography or cerebral angiography. These slow body movements may even include a brief attempt of the body to flex at the waist, making it seem to rise. The arms may be raised independently or together. Forceful flexion of the neck or rotation of the body may initiate these movements. Legs seldom move spontaneously, although in two patients, "stepping movements" (an exaggerated triple flexion) were noted just before brain death.[24] Other manifestations that have been reported are a slow turning of the head to one side, an undulating toe sign (snapping the big toe leads to an undulating movement of the toes),[25] facial twitching,[21] a persistent Babinski reflex, and tendon, abdominal, and cremasteric reflexes.

NEUROLOGIC STATES THAT CAN MIMIC BRAIN DEATH

Misdiagnosis of brain death is possible if a locked-in syndrome,[26] hypothermia,[27] or drug intoxication[28-30] is not recognized. The locked-in syndrome is usually a consequence of the destruction of the base of the pons. The patient cannot move the limbs, grimace, or swallow, but the upper rostral mesencephalic structures involved in voluntary blinking and vertical eye movements remain intact. Consciousness persists because the tegmentum, with the reticular formation, is not affected. The condition is most often caused by an acute embolus to the basilar artery.[26] More dramatic is the reversible Guillain–Barré syndrome involving all the peripheral and cranial nerves. The progression occurs over a period of days, and knowledge of the history should prevent the dangerous error of diagnosing brain death.[31]

Accidental hypothermia from prolonged environmental exposure may mimic loss of brain function, but alcohol intoxication and head injury are often major confounders.[27] Hypothermia causes a downward spiral of loss of brain-stem reflexes and pupillary dilatation. The response to light is lost at core temperatures

TABLE 2. CONFIRMATORY TESTING FOR A DETERMINATION OF BRAIN DEATH.

Cerebral angiography

The contrast medium should be injected under high pressure in both anterior and posterior circulation.
No intracerebral filling should be detected at the level of entry of the carotid or vertebral artery to the skull.
The external carotid circulation should be patent.
The filling of the superior longitudinal sinus may be delayed.

Electroencephalography

A minimum of eight scalp electrodes should be used.
Interelectrode impedance should be between 100 and 10,000 Ω.
The integrity of the entire recording system should be tested.
The distance between electrodes should be at least 10 cm.
The sensitivity should be increased to at least 2 μV for 30 minutes with inclusion of appropriate calibrations.
The high-frequency filter setting should not be set below 30 Hz, and the low-frequency setting should not be above 1 Hz.
Electroencephalography should demonstrate a lack of reactivity to intense somatosensory or audiovisual stimuli.

Transcranial Doppler ultrasonography

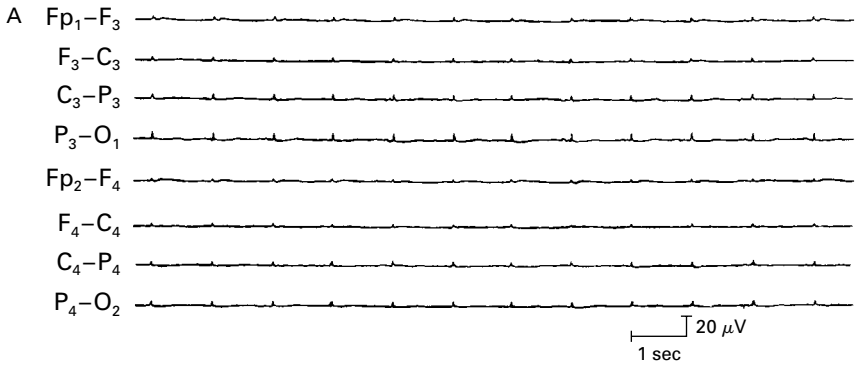
There should be bilateral insonation. The probe should be placed at the temporal bone above the zygomatic arch or the vertebrobasilar arteries through the suboccipital transcranial window.
The abnormalities should include a lack of diastolic or reverberating flow and documentation of small systolic peaks in early systole. A finding of a complete absence of flow may not be reliable owing to inadequate transtemporal windows for insonation.

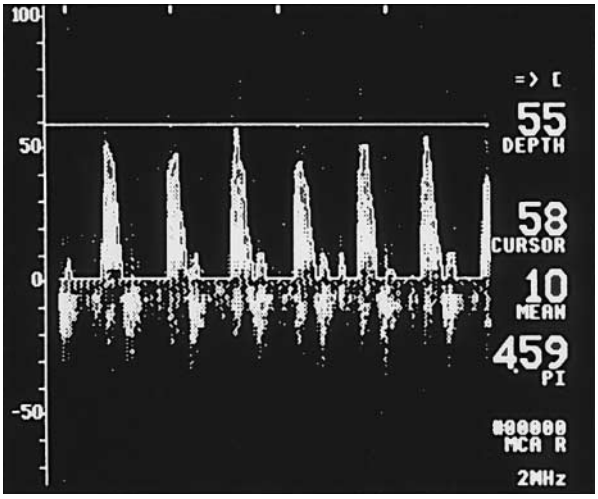
Cerebral scintigraphy (technetium Tc 99m hexametazime)

The isotope should be injected within 30 minutes after its reconstitution.
A static image of 500,000 counts should be obtained at several time points: immediately, between 30 and 60 minutes later, and at 2 hours.
A correct intravenous injection may be confirmed with additional images of the liver demonstrating uptake (optional).

Figure 2 (facing page). Examples of Bedside Tests to Confirm Brain Death.

Panel A shows an isoelectric electroencephalogram in which the only pulse is artifactual. Shown is a bipolar montage with the electrodes placed according to 10/20 configuration. Transcranial Doppler ultrasonograms show reverberating flow (Panel B) and small systolic peaks (Panel C), both of which are patterns seen in patients with massively increased intracranial pressure that can also be seen when brain death has occurred. In Panel D, a dynamic nuclear scan shows no intracranial filling — the so-called hollow-skull sign.





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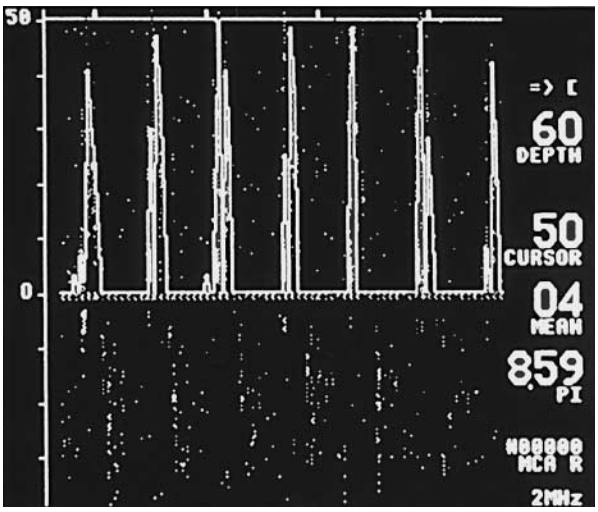

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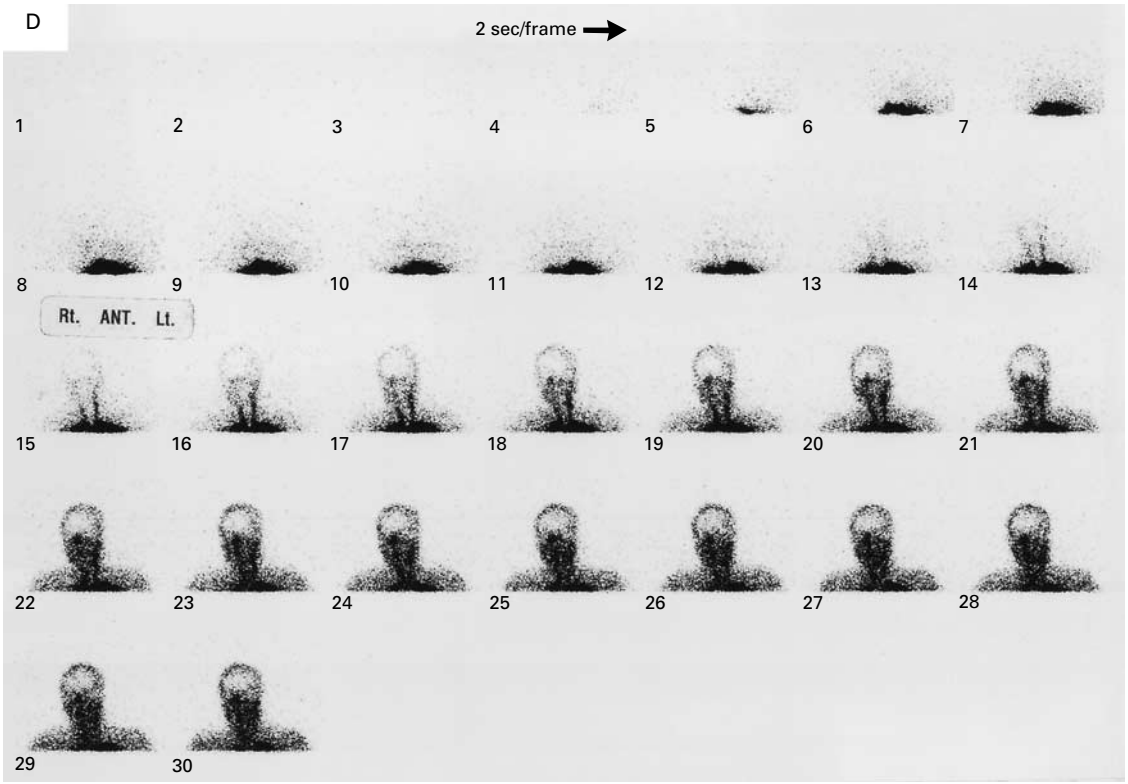

of 28°C to 32°C, and brain-stem reflexes disappear when the core temperature drops below 28°C.[27] These deficits are all potentially reversible, even after extreme hypothermia.[32]

The effects of many sedative and anesthetic agents can closely mimic brain death, but aspects of brain-stem function, particularly the pupillary responses to light, remain intact. When ingested in large quantities, many drugs can cause a partial loss of brain-stem reflexes. Formal determinations of brain death documenting conditions that are entirely similar to those caused by structural lesions are exceptional but have been reported in cases of intoxication with tricyclic antidepressants and barbiturates.[28,29] A more complex problem is the possible confounding of the clinical determination of brain death by metabolites or traces of circulating pharmaceutical agents. Screening tests for drugs may be helpful, but some toxins (e.g., cyanide, lithium, and fentanyl) may not be detected by routine screening tests.[29] A clinical diagnosis of brain death should be allowed if drug levels (e.g., of barbiturates used to treat increased intracranial pressure) are below the therapeutic range. A reasonable approach is as follows: If it is known which drug or poison is present but the substance cannot be quantified, the patient should be observed for a period that is at least four times the elimination half-life of the substance, provided that the elimination of the drug is not interfered with by other drugs or organ dysfunction. If the particular drug is not known but high suspicion persists, the patient should be observed for 48 hours to determine whether a change in brain-stem reflexes occurs; if no change is observed, a confirmatory test should be performed.

CONFIRMATORY TESTS

Confirmatory tests (Table 2) are optional in adults but recommended in children younger than one year old.[33] In several European, Central and South American, and Asian countries, confirmatory testing is required by law. Certain countries (e.g., Sweden) require only cerebral angiography. In the United States, the choice of tests is left to the discretion of the physician, but bedside tests seem to be preferred.

Cerebral angiography may document nonfilling of the intracranial arteries at the entry to the skull because the systolic pressure is not high enough to force blood through the intracranial vascular tree.[34] Perivascular glial swelling and the formation of subintimal blebs caused by ischemia may cause the collapse of smaller vessels, leading to increased intravascular resistance.[35] Cerebral angiography is performed with an injection in the aortic arch to visualize both the anterior and the posterior circulation. Arrest of flow is found at the foramen magnum in the posterior circulation and at the petrosal portion of the carotid artery in the anterior circulation.[34] Magnetic resonance angiography may produce similar views.

Electroencephalography is used in many countries and remains one of the most well-validated confirmatory tests. Recordings are obtained for at least 30 minutes with a 16- or 18-channel instrument. In a patient who is brain dead, electrical activity is absent at levels higher than 2 μV with the instrument set at a sensitivity of 2 μV per millimeter (Fig. 2A).[36,37] However, the high levels of sensitivity set on the electroencephalography machine increase artifacts, which are plentiful in the intensive care unit because of the presence of multiple devices.

Transcranial Doppler ultrasonography has a sensitivity of 91 to 99 percent and a specificity of 100 percent.[38] A portable, 2-Hz, pulsed-wave Doppler ultrasonographic instrument is used, insonating both middle cerebral arteries and vertebral arteries. The absence of a signal may be artifactual if a bone window interferes with insonation. In patients who are brain dead, transcranial Doppler ultrasonography typically reveals the absence of the diastolic or reverberating flow that is caused by the contractive force of the arteries; the pulsatility index is very high, with systolic velocities that are only a fraction of the normal level (Fig. 2B and 2C).[39,40]

Nuclear imaging with technetium may demonstrate an absence of intracerebral uptake of the tracer (Fig. 2D).[41] The correlation with conventional angiography is good. The diagnostic criteria of the most commonly used confirmatory tests are described more fully in Table 2.

CONCLUSIONS

After the clinical criteria of brain death have been met, the physician should inform the next of kin, who can be approached about organ donation.[42] The physician is required to abide by state law with respect to organ donation. In the United States, organ-procurement agencies must be notified to request the donation of organs. If the legal next of kin declines to donate organs, it is good medical judgment to discontinue mechanical ventilation.

When mechanical ventilation and support are continued because of ethical or legal objections to their discontinuation, what usually follows is an invariant heart rate from a differentiated sinoatrial node, structural myocardial lesions leading to a marked reduction in the ejection fraction, decreased coronary perfusion, the need for increasing use of inotropic drugs to maintain blood pressure, and a fragile state that leads to cardiac arrest within days or weeks.[43]

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