Diagnosis of brain death

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INTRODUCTION

Death is an irreversible, biologic event that consists of permanent cessation of the critical functions of the organism as a whole [1]. This concept allows for survival of tissues in isolation, but it requires the loss of integrated function of various organ systems. Death of the brain therefore qualifies as death, as the brain is essential for integrating critical functions of the body. The equivalence of brain death with death is largely, although not universally, accepted [2].

Brain death implies the permanent absence of cerebral and brainstem functions. Although the term "brain dead" is often used colloquially and to extend to all those with severe brain damage and those in vegetative states, in medical-legal terms, its meaning is very specific. Persistent vegetative state is described elsewhere. (See "Hypoxic-ischemic brain injury in adults: Evaluation and prognosis".)

The concept of brain death, or the complete, irreversible cessation of brain function, including the capacity for brainstem, respiratory, and vegetative activities, was first described in 1959, predating widespread organ donation; although the latter made its codification critically necessary. While most countries have a legal provision for brain death, institutional protocols for diagnosis are not universal and are often absent, particularly in lower-income countries and in those without an organized transplant network [3]. Even among countries with an organized diagnostic protocol, there is substantial variation in the criteria that are used.

While United States law equates brain death with cardiopulmonary death, specific criteria for diagnosis are not mandated [4]. Some states and institutions have specific diagnostic mandates, especially when applied to organ donor candidates. Most clinicians rely on published guidelines [5,6]. However, a 2007 survey of prominent neurologic institutions in the United States found that there was considerable variability in adherence to published guidelines and clinical practice [7]. Variable documentation of brain death criteria was also observed in a series of 142 children referred for organ donation [8], and in a chart review of 226 organ donors collected from 68 hospitals in the midwest United States [9].

In most adult series, trauma and subarachnoid hemorrhage are the most common event leading to brain death [10-12]. Others include intracerebral hemorrhage, hypoxic-ischemic encephalopathy, and ischemic stroke. Any condition causing permanent widespread brain injury can lead to brain death.

CLINICAL CRITERIA

The diagnosis of brain death can usually be made clinically, at the bed side. The criteria for brain death require certain conditions regarding the clinical setting as well as evidence of absence of brain function on neurologic examination.

Clinical setting — There are a number of prerequisites before one can begin considering a patient "brain dead" [5,6,13]:

- Clinical or neuroimaging evidence of an acute central nervous system (CNS) catastrophe that is compatible with the clinical diagnosis of brain death (ie, the cause of brain death should be known).
- Exclusion of complicating medical conditions that may confound clinical assessment (no severe electrolyte, acid-base, endocrine, or circulatory [ie, shock] disturbance).
- No drug intoxication or poisoning, which may confound the clinical assessment.
- Core temperature >36°C (97°F). Hypothermia may also confound the diagnostic assessment of brain death and can also delay the increase in $PaCO_2$ necessary to complete the apnea test [6,14-16]. A warming blanket is required to achieve normothermia in many patients with brain death. There is little evidence base for a choice of threshold temperature. Canadian forum recommendations published in 2006 use 34°C as a standard [17].
- Normal systolic blood pressure >100 mmHg. Vasopressors may be required.

Neurologic examination — The examination must demonstrate absent cerebral or brainstem function with all of the following findings [5,13]:

- Coma

- Absent brain-originating motor response, including response to pain stimulus above the neck or other brain-originating movements (eg, seizures, decerebrate or decorticate posturing)
- Absent pupillary light reflex; pupils are midposition or dilated (4 to 9 mm)
- Absent corneal reflexes
- Absent oculovestibular reflexes (caloric responses)
- Absent jaw jerk
- Absent gag reflex
- Absent cough with tracheal suctioning
- Absent sucking or rooting reflexes
- Apnea as demonstrated by apnea test, described below

The technique for examination of the cranial nerve reflexes is described elsewhere. (See "Stupor and coma in adults", section on 'Cranial nerves'.)

The depth of coma must be assessed by documenting absent alerting and absent movements arising from the brain, either spontaneous or stimulus induced. Brain-originating movements include cortically originating complex, purposeful movements, and also decerebrate or decorticate posturing, facial grimacing, and seizures.

Movements originating from the spinal cord or peripheral nerve may occur in brain death [6]. These are common (33 to 75 percent) and may be triggered by tactile stimuli or occur spontaneously [10,18,19]. Examples include:

- Subtle, semirhythmic movements of facial nerve-innervated muscles can arise from the denervated facial nerve.
- Finger flexor movements.
- Tonic neck reflexes – Passive neck displacements, especially flexion, may be accompanied by complex truncal and extremity movements, including adduction at the shoulders, flexion at the elbows, supination or pronation at the wrists, flexion of the trunk ("sitting up" type movements), and neck-abdominal muscle contraction or head turning to one side. These might be quite dramatic, often called a "Lazarus sign."
- Triple flexion response with flexion at the hip, knee, and ankle with foot stimulation (eg, testing for a Babinski sign).

- Other truncal movements including asymmetrical opisthotonic posturing of the trunk and preservation of superficial and deep abdominal reflexes.
- Alternating flexion-extension of the toes with passive displacement of the foot (undulating toe sign), or flexion of the toes after foot percussion, or a Babinski sign.
- Upper limb pronation extension reflex.
- Widespread fasciculations of trunk and extremities [20].

Apnea test

Standard procedure

Standard procedure — The apnea test is performed after all other criteria for brain death have been met. Core temperature ≥36°C or 97°F, systolic blood pressure ≥100 mmHg, eucapnia ($PaCO_2$ 35 to 45 mmHg), absence of hypoxia, and euvolemic status are prerequisites [5,6]. The test is not valid in patients who chronically have high $PaCO_2$ values (CO_2 retainers) and in cases of neuromuscular paralysis or high cervical spinal cord lesions. In a positive apnea test there is no respiratory response to a $PaCO_2$ >60 mmHg or 20 mmHg greater than baseline values and a final arterial pH of <7.28.

Disconnecting the ventilator is often associated with profound hypoxemia and hemodynamic instability. This can be obviated by increasing inspired oxygen before and during the test. Preoxygenation eliminates stores of respiratory nitrogen and accelerates oxygen transport through the tracheal cannula [5,6]. The fraction of inspired oxygen should be 1.0 for 10 minutes, up to a maximum PaO_2 of 200 mmHg or until the $PaCO_2$ exceeds 40 mmHg. Ventilation frequency is reduced to eucapnia; positive end-expiratory pressure is reduced to 5 cm H_2O. If SaO_2 >95 percent, then an arterial blood gas (ABG) is obtained. The patient is then disconnected from the ventilator. Oxygen is provided by a tracheal cannula at 6 L/minute; the tip should lie at the carina. Alternatives include using a T-piece system with oxygen flow at 12 L/minute and using continuous positive airway pressure (CPAP) 10 to 20 cm H_2O, with oxygen flow at 12 L/minute [21,22].

Visual observation is the standard method for detecting respiratory movement [6]. Eight to 10 minutes with no observable respiratory effort is a standard observation period. $PaCO_2$ is measured just prior to reconnection to the ventilator to confirm that the target level (>60 mmHg or 20 mmHg greater than baseline values) was achieved.

Challenges and test modification — Hypotension (systolic blood pressure <90 mmHg), hypoxemia (SaO_2 <85 percent for >30 seconds), or cardiac arrhythmia may occur during the apnea and lead to abortion of the apnea test. These events may suggest inadequate oxygenation or preoxygenation, or baseline cardiopulmonary disease. While complications precluding the completion of the apnea test have been reported to occur in 10 to 26 percent of individuals [11,12], a more recent study found that with appropriate prerequisites (adequate preoxygenation, no acid-base or electrolyte abnormalities, normotension, and stable cardiac rhythm), the apnea test was completed without complication in most (62 of 63) patients [11]. When aborted, the test can be reattempted using CPAP as described above; in one series this method allowed completion of the apnea test in 2 of 20 patients who could not complete it using tracheal cannula oxygen supply [21]. Ancillary tests are necessary if the apnea test cannot be completed. (See 'Ancillary tests' below.)

An innovation in the apnea test involves introducing 3 to 5 percent CO_2 along with oxygen and providing approximately four breaths per minute using a ventilator that is capable of detecting respiratory effort, while monitoring the end-tidal CO_2 concentration [23]. However, other authors have criticized CO_2 supplementation techniques because rates of $PaCO_2$ accumulations may be unpredictable, excessive hypercarbia can cause complications, and more gradual increases in $PaCO_2$ may not effectively stimulate respiratory centers [11]. $PaCO_2$ increases at a rate of 2.5 to 3 mmHg per minute in traditional testing.

Case reports have drawn attention to potential diagnostic confusion that may arise in the setting of spurious ventilator triggering by patients with apnea test-confirmed brain death [24-26]. Sensitive flow trigger settings on new-generation ventilators lead to ventilator self-cycling, which may be misinterpreted as respiratory effort. Increasing the trigger flow sensitivity threshold or changing to a pressure trigger mechanism eliminates this phenomenon. However, determination of apnea can only be assessed reliably by disconnecting the ventilator as described above [6].

False evidence of spontaneous breathing has also been reported, even before apnea testing is performed, on patients on pressure support ventilation in which the threshold for triggering the ventilator is set so low that a hyperdynamic precordium can lead pressure changes to cause the ventilator to provide "breaths" with low threshold settings [27]. Formal apnea testing should be performed if this phenomenon seems likely.

The apnea test requires modification in patients who have been resuscitated using extracorporeal membrane oxygenation (ECMO), but has been shown to be feasible in a number of case reports [28,29]. One literature review summarizes a procedure that includes decreasing the sweep rate to achieve hypercapnia, maintaining oxygenation through oxygen circuit delivery or by supplementation through the endotracheal tube, maintenance of CPAP and hemodynamic support with circuit pump flow, and vasoactive medications as needed [28].

Observation period — The length of observation required to determine brain death varies extensively. A follow-up evaluation after 24 hours was an early requirement for brain death diagnosis in the United States. Later, requirements in this regard were made age dependent: a 48-hour evaluation interval for infants age seven days to two months, 24 hours for those greater than two months to one year, and 12 hours for those between 1 and 18 years. (See 'Brain death in children' below.).

An observation period for adults is considered optional; six hours is often recommended, with longer periods, up to 24 hours, recommended in cases of hypoxic-ischemic encephalopathy [5]. Guidelines in other countries recommend longer observation periods [3,30]. The American Academy of Neurology guideline update published in 2010 found insufficient evidence to determine a minimally acceptable observation period [6]. In patients who have been resuscitated after cardiac arrest, we recommend observation for at least 24 hours from the time of the arrest, as spontaneous improvement in brainstem reflexes can occur hours after cardiac arrest. In such patients who have received induced hypothermia, the recovery time may be further extended, as some motor and brainstem reflexes may recover after being absent for three days [31]. It may be advisable to perform an ancillary test of brain blood flow with such patients; electrophysiologic parameters may also be affected by induced hypothermia. (See "Hypoxic-ischemic brain injury in adults: Evaluation and prognosis".)

There are limited studies of serial examinations in this setting upon which to base recommendations for a required length of observation [6]. One case series reviewed data from 1229 adult and 82 pediatric (greater than one year of age) cases of brain death [32]. The interval between first and second examinations ranged from 3 to over 50 hours (mean 19.2 hours). None of the patients with an initial examination consistent with brain death regained brainstem function on repeat examination. However, rates of organ donation decreased with longer intervals between examinations.

Examiner(s) — The expertise of the examiners required to make a diagnosis of brain death varies by state and country [3,5,6]. Some states (eg, Virginia) specifically require the physician to be a specialist in the neurosciences, while others (Alaska, Georgia) give authority to nurses with subsequent certification by a physician. States and countries also differ as to whether more than one physician is required to certify a patient as brain dead [3,30].

The examiner making the diagnosis of brain death should be familiar with the clinical criteria and comfortable in performing all aspects of the examination. A systematic review of the literature found that the precision of the neurologic examination in comatose patients is moderate to substantial; only one study found diminished precision in less-experienced examiners [33]. Simulation-based training may improve the examiner's performance, at least in the short term [34].

Another common requirement or recommendation is that the brain death examiner be someone other than the treating physician. In addition, when organ donation is being considered, the examiner should not be the same physician or surgeon who is part of the transplant team or has responsibilities to the potential recipient of one or more organs [17,30,35].

ANCILLARY TESTS

Indications — A valid, complete clinical examination is sufficient and superior to diagnostic testing in the diagnosis of brain death in adults. However, sometimes the clinical criteria cannot be applied. Such situations include the following [6]:

- When the cranial nerves cannot be adequately examined
- When neuromuscular paralysis is present
- When heavy sedation is present
- When the apnea test is not valid (high carbon dioxide retainers) or cannot be completed
- When confounders render the clinical examination unreliable (eg, multiple organ failure and the presence of a sedating or paralyzing drug that may be very slow to clear)
- To shorten the duration of the observation period

In these situations, ancillary tests are necessary. Ancillary testing is also required for infants less than one year; two positive tests are required for those less than two months of age. Other countries mandate the use of confirmatory tests to supplement the clinical examination [3,30].

Choice of test — An ideal ancillary test for brain death should meet all of the following criteria:

- There should be no "false positives" (ie, when the test confirms "brain death" there should be none that recover or have the potential to recover)
- The test should be sufficient on its own to establish that brain death is or is not present (ie, whether there is total and irreversible destruction of the brainstem or the entire brain)
- The test should not be susceptible to "confounders" such as drug effects or metabolic disturbances
- The test should be standardized in technology, technique, and classification of results
- The test should be available, safe, and readily applied in all medical centers with intensive care units (ICUs)

Unfortunately, no currently available test for brain death meets all of these criteria. Studies examining their utility are limited; they are generally quite small and often examine only clinically brain dead individuals, not allowing for detection of false-positive errors. Individual tests have different strengths and weaknesses in different clinical situations, which may guide their selection.

Cerebral angiography best approximates a "gold standard" but is invasive, risky, and may be inaccurate (as are other tests of blood flow) in profound hypotension and when the cranial vault is breached by trauma, surgery, ventricular drain, or open cranial sutures. Under these circumstances an electrophysiologic test (electroencephalography [EEG] or somatosensory evoked potentials [SSEP]) may be superior. However, tests of cerebral blood flow are less subject to confounding by hypothermia, drugs, and metabolic factors than are electrophysiologic tests. For this reason, tests of cerebral blood flow are the most useful in those clinical settings in which the clinical criteria cannot be applied. SSEPs should not be used if the primary pathology is in the brainstem or in the setting of underlying neuropathy. EEG, evoked potentials (EPs), and transcranial Doppler (TCD) may be done at the bedside. The availability of different testing modalities and the requisite experience and expertise differ among institutions.

Brain blood flow — Tests demonstrating absent blood flow to the brain are generally accepted as establishing whole brain death; it is axiomatic that the brain without a blood supply is dead. It does not always follow that the presence of some arterial blood flow in the intracranial compartment precludes the diagnosis of brain death.

Brain death is usually accompanied by elevated intracranial pressure from tissue edema or other mass effect. When this exceeds systemic arterial pressure, there is no cerebral blood flow.

Some intracranial arterial filling at the base of the brain without tissue perfusion can be seen in brain death, producing a "false-negative" test result for brain death. More refined techniques that examine brain perfusion are likely to be more accurate. Such tests include computed tomography (CT) perfusion studies (not widely available) [36], radionuclide studies (see 'Nuclear medicine' below) [37], and magnetic resonance perfusion studies [38-41]. Absent opacification of deep cerebral veins on conventional or CT angiography (CTA) may be more sensitive for brain death than filling of cerebral arteries [42,43]. (See 'Computed tomographic angiography' below.)

Tests of blood flow may also be subject to false-negative error early on when trauma, surgery, ventricular drain, and open cranial sutures lower intracranial pressure.

Widely available tests of cerebral blood flow include cerebral angiography, TCD, magnetic resonance angiography (MRA), CTA, and nuclear medicine radionuclide scanning. These tests are not confounded by drugs, metabolic disorders, or hypothermia. A caveat is that the systemic blood pressure should be adequate (ie, the patient should not be in shock) when these tests are applied.

Cerebral angiography — Four-vessel conventional cerebral angiography is the traditional gold standard among cerebral blood flow tests for brain death. The test is invasive and requires transportation to the radiology department. Blood pressure must be monitored during the procedure, as patients are often hemodynamically unstable. In addition, a severely damaged brain may have lost autoregulation, causing blood flow to vary with changes in perfusion pressure.

In cases of brain death, cerebral angiography usually demonstrates absent blood flow at or beyond the carotid bifurcation or circle of Willis. The external carotid system should be patent. In a minority of cases, angiography may demonstrate contrast stasis or delayed filling in intracranial arteries, perhaps as an evolutionary stage preceding absent filling [44,45]. False-negative cerebral angiograms showing normal-appearing blood flow in at least some intracranial blood vessels are reported to occur when intracranial pressure is lowered by surgery, trauma, and ventricular shunts or in infants with pliable skulls.

Transcranial Doppler — TCD is safe, noninvasive, and inexpensive, and it can be done at the bedside. The test requires expertise; both anterior and posterior circulations should be evaluated [46]. Findings of small systolic peaks without diastolic flow or a reverberating flow pattern suggest high vascular resistance and support the diagnosis of brain death. Limitations include a 10 to 25 percent prevalence of temporal bone thickening that precludes evaluation of 6 of the usual 11 insonated intracranial arteries. Because of these and other technical limitations, absence of arterial signals on TCD (a finding in 9 percent of brain dead patients) is considered nondiagnostic [47,48]. Both false-positive and false-negative tests (compared with cerebral angiography or other standard) are reported [49-51].

As with cerebral angiography, patients with external ventricular drains or large craniotomies may have false-negative testing [45,51,52]. Caution should also be exercised with very young children, at least until further studies are done in this population.

In one study comparing 61 patients with clinical brain death with 39 control patients in coma but not brain dead, the sensitivity of TCD was 70.5 percent, and the specificity was 97.4 percent [53]. Similar results were observed in a case-control study of 101 comatose patients in which it was also observed that both sensitivity and specificity improved over time to 100 percent for examinations performed 24 hours or more after clinical diagnosis of brain death [46].

Magnetic resonance angiography — Absence of arterial blood flow on MRA supports the diagnosis of brain death. In addition, magnetic resonance imaging (MRI) also shows variable degrees of cerebral edema and mass effect. Small case series and one case control study suggest that it is a sensitive test for brain death, but has uncertain specificity [6,54-56]. Disadvantages include that patients are required to lie flat and that there may be short periods of time in which clinical monitoring is impossible, making this somewhat problematic in unstable patients.

Computed tomographic angiography — The clinical utility of CTA and CT perfusion in the evaluation of brain death is uncertain, but appears to be similar to other ancillary studies. These tests are somewhat more invasive than MRA, in that contrast injection is required. Case reports document findings of absent cerebral circulation perfusion on CTA in patients with brain death [57-60]. However, systematic reviews of studies comparing CTA with an alternative brain death determination have concluded that the reported sensitivities are variable and appear low overall (ranging from 62 to 99 percent) [61,62]. The highest sensitivity was achieved when the absence of opacification of the internal cerebral veins was used as a criterion [42]. The absence of studies examining CTA findings in patients who are comatose but not brain dead precludes an assessment of this test's specificity [6,62]. In one series of 18 patients undergoing evaluation for brain death, the sensitivity and specificity of CTA was 75 and 100 percent, respectively, when compared with either clinical examination and/or conventional angiography; all nine patients who underwent both CTA and conventional angiography had concordant results [63].

Nuclear medicine — The most common radionuclide modality for brain imaging uses the tracer, 99mTc-labeled hexamethylpropyleneamine oxime (HMPAO), and subsequent imaging with single-photon emission computed tomographic (SPECT) brain scintigraphy. The tracer penetrates into the brain parenchyma in proportion to regional blood flow and shows no significant redistribution for several hours, making it easy to perform and interpret imaging [64]. The absence of isotope uptake ("hollow skull phenomenon") indicates no brain perfusion and supports the diagnosis of brain death (figure 1) [37].

Studies find that HMPAO-SPECT is useful in the diagnosis of brain death [65-68]. The sensitivity improves on follow-up examination in 24 to 48 hours [67,68]. In studies with small "control" groups of brain injured, but not brain dead individuals, there were no false-positive studies [66,67]. HMPAO-SPECT also appears to be useful in pediatric patients, although the examination in very young infants with open cranial sutures also appears to be subject to false-negative error, at least on initial examination [69]. A false-positive appearance of absent brain blood flow was described in an infant in whom brain blood flow was assessed by SPECT in a single imaging plane; this emphasizes the importance of imaging in both anterior and lateral views [70].

Electrophysiology — Electrophysiologic tests used in the diagnosis of brain death include EEG and EPs.

Electroencephalography — Electrocerebral silence or a flat EEG was a component of brain death declaration with the first guidelines published. Electrocerebral silence is present if no nonartifactual electrical potential >2 microvolts is found during a 30-minute recording at increased sensitivity [71]. EEG remains strongly recommended in the United States and is an essential part of the American criteria for the diagnosis of brain death in very young children [72]. However, although the flat or suppressed recording prompts clinicians to consider brain death, EEG is anatomically and physiologically limited for this purpose.

The EEG records summated synaptic potentials from the cerebral neocortex and does not reveal potentials from subcortical structures, such as the brainstem or thalamus. Hence, the EEG may be flat or isoelectric in the presence of viable neurons in the brainstem and elsewhere. The EEG is also vulnerable to confounders, and it may be flat or isoelectric in cases of sedation from medication or toxic ingestion, hypothermia, or metabolic factors (conditions that do not necessarily imply complete and irreversible brain injury). A number of false-positive cases of flat EEG recordings in these situations have been reported [73,74]. In addition, especially in the ICU, some electrical signals are recorded for which the source cannot be identified, even though they probably do not arise from the brain [75]. Such artifacts may be mistaken for residual cortical activity, producing a false-negative error.

Evoked potentials — SSEPs and brainstem auditory evoked potentials (BAEPs) also have limited utility as ancillary tests [76-78]. In SSEPs, the bilateral absence of the parietal sensory cortex responses (N19-P22) in response to median nerve stimulation is supportive of brain death. The absence of brainstem responses to an auditory stimulus (Waves III to V) in the presence of preserved cochlear response (Wave I) is required for a BAEP result to support the diagnosis of brain death.

Each test activates a discrete sensory pathway and extends the electrophysiologic interrogation beyond the EEG to areas of interest in the brainstem. However, these are highly specific, restricted pathways; EPs do not test the functional integrity of other central nervous system (CNS) structures. For both SSEP and BAEP, restricted proximal lesions, including those outside the CNS, may eliminate cortical response. Cases of preserved EEG integrity in the face of absent EPs have been described in individuals with primary brainstem pathology [79].

Unlike EEG signals, the early components of SSEPs and BAEPs are minimally affected by sedative drugs and anesthetics [80]. However, hypothermia, drugs, and metabolic derangements can affect middle and late somatosensory and auditory potentials [81]. Some have argued that the combination of BAEPs and SSEPs with EEG offers greater assurance of an accurate diagnosis of brain death [79]. However, the requirement for an intact Wave I in the BAEP limits its broad applicability, as the cochlear end organ is frequently damaged in trauma.

One series of EP testing in 130 clinically brain dead patients (ages 8 to 77 years) showed that BAEPs provided information in 29.2 percent [79]. In these patients, BAEP excluded brain death in 4.6 percent, while confirming the diagnosis in 24.6 percent. In the same 130 patients, SSEPs were useful in 97 percent, confirmed brain death in 94 percent, and excluded the diagnosis in 3 percent [79]. A cohort study of 181 comatose patients found that the P14 responses on SSEP were uniformly absent in all 108 brain dead patients and uniformly present in the remaining non-brain dead patients [82]. Similar results have been shown in a primary pediatric population [83].

Other tests — The atropine test examines the heart rate response to intravenous injection of 3 mg atropine. An increase in heart rate of <3 percent supports the diagnosis of brain death [84,85]. As the dorsal motor vagal nucleus is in the medulla, the test provides a limited assessment of caudal medullary function. Although this is probably one of the last functions to be lost in brain death, the test provides a very restricted assessment and has not been widely validated.

In a study of 118 brain dead patients and 152 survivors of severe brain injury, the ratio of venous oxygen concentration in the right atrium compared with the jugular bulb was shown to have 96.6 percent sensitivity and 99.3 percent specificity for brain death [86]. The test is not available in many centers, carries a small risk, and requires special training for catheter insertion.

BRAIN DEATH MIMICS

Misdiagnosis of brain death has been reported in the following clinical scenarios:

- Locked-in syndrome [87]
- Neuromuscular paralysis, as found in severe, acute polyneuropathies (some may also have autonomic dysfunction, including pupillary areflexia) or with neuromuscular blocking agents
- Hypothermia [88]
- Drug intoxication [89]
- Guillain-Barré syndrome [90,91]

The locked-in syndrome is a consequence of a focal injury to the base of the pons, usually by embolic occlusion of the basilar artery [87]. Consciousness is preserved; however, the patient cannot move muscles in the limbs, trunk, or face, except that voluntary blinking and vertical eye movements remain intact. Patients with this syndrome have been mistakenly believed to be unconscious [92]. Patients with primary brainstem pathology who are believed to be brain dead should be carefully examined to ensure that they are not instead locked-in. (See "Locked-in syndrome".)

The other entities listed, as well as other potential brain death mimics (eg, metabolic encephalopathy) may produce a neurologic examination consistent with brain death, but they should not be mistaken for brain death if the other criteria are applied. (See 'Clinical setting' above.)

BRAIN DEATH IN CHILDREN

Brain death in children most commonly occurs as a result of trauma and anoxic encephalopathy [93]. Infections and cerebral neoplasms are other causes. United States guidelines for criteria for brain death in children were updated in 2011 [94]. These are:

- The diagnosis of brain death cannot be made in preterm infants less than 37 weeks gestational age.

- Hypotension, hypothermia, and metabolic disturbances should be treated and corrected, confounders should be excluded, and medications that can interfere with the neurologic examination and apnea testing should be discontinued, with time allowed for adequate clearance before proceeding with the evaluation.

- Two examinations including apnea testing with each examination separated by an observation period are required. Examinations should be performed by different attending physicians. Apnea testing may be performed by the same physician. An observation period of 24 hours for term newborns to 30 days of age, and 12 hours for infants and children (30 days to 18 years) is recommended. Assessments in neonates and infants should be performed by pediatric specialists with critical care training.

  The first examination determines the child has met the accepted neurologic examination criteria for brain death. The second examination confirms brain death based on an unchanged and irreversible condition. (See 'Neurologic examination' above.)

  Assessment of neurologic function following cardiopulmonary resuscitation or other severe acute brain injuries should be deferred for 24 hours or longer if there are concerns or inconsistencies in the examination.

- Apnea testing to support the diagnosis of brain death requires documentation of an arterial $PaCO_2$ 20 mmHg above the baseline and ≥60 mmHg with no respiratory effort during the testing period (see 'Apnea test' above). If the apnea test cannot be safely completed, an ancillary study should be performed.

- Ancillary studies (electroencephalography [EEG] and radionuclide cerebral blood flow) are not required to establish brain death and are not a substitute for the neurologic examination (see 'Ancillary tests' above). Ancillary studies may be used to assist in making the diagnosis of brain death:

  - When components of the examination or apnea testing cannot be completed safely due to the underlying medical condition of the patient

  - If there is uncertainty about the results of the neurologic examination

- If a medication effect may be present
- To reduce the interexamination observation period

When ancillary studies are used, a second clinical examination and apnea test should be performed and components that can be completed must remain consistent with brain death. In this instance the observation interval may be shortened and the second neurologic examination and apnea test (or all components that are able to be completed safely) can be performed at any time thereafter.

These guidelines are based in large part on consensus opinion, as evidence is limited. As a result, they are somewhat controversial and criteria vary worldwide [3,95]. Some believe that a diagnosis of brain death cannot be made reliably in very young infants. Committees in the United Kingdom, Australia, and New Zealand decided to declare brain death only in children ≥2 months in age.

Recommendations from a Canadian forum published in 2006 had somewhat different qualifications regarding the brain death criteria for children [17]:

- Full-term newborns >48 hours and <30 days old must have serial determinations separated by 24 hours. Clinical criteria should additionally include absent oculocephalic and suck reflexes. The minimum body temperature must be ≥36°C. Ancillary tests are required for presence of confounders or inability to establish clinical criteria.
- For infants 30 days to one year, clinical criteria should use oculocephalic rather than the oculovestibular reflex. A second examiner should confirm the diagnosis, but no time interval is specifically required. Ancillary tests are required only for clinical uncertainty or confounding factors.
- For children greater than one year, a second examiner should confirm the diagnosis if organ donation is planned as required by law. No time interval is required.

PROGNOSIS

In adults, there are no published reports of recovery of neurologic recovery after a diagnosis of brain death as outlined above [6,13]. (See 'Clinical setting' above.)

In adults, brain death rarely lasts for more than a few days before it is followed by somatic death. Brain ischemia leads to sympathetic nervous system collapse, leading to vasodilation and cardiac dysfunction [96]. In most patients, blood pressure rapidly declines even with the use of intravenous vasopressor therapy [97]. Pulmonary edema and diabetes insipidus are frequent early consequences of brain death and may also precipitate cardiopulmonary failure [98]. In one series, all 73 patients meeting the clinical criteria for brain death suffered cardiac asystole despite full cardiorespiratory support; 97 percent died within seven days [99]. Most clinicians feel that the diagnosis of brain death is doubtful in the face of prolonged clinical stability [100].

One case series of 175 patients surviving longer than one week after diagnosis of brain death challenges this tenet [101]. In this series, 80 patients survived two weeks, 44 survived four weeks, 20 survived two months, and seven survived six months. Those with long survivals were very young (two newborns). The validity of the sources and brain death diagnoses in these patients has been challenged [102]. However, there is at least one case of a 13-year-old with well-documented brain death who remains on life support for more than one year [103].

Some patients have religious beliefs that oppose the equivalence of brain death with death. The states of New Jersey and New York have dealt with this by passing laws that require cardiopulmonary death as the definition of death in these patients. There may be other sources of controversy. While there is legal precedent for discontinuing life support over the family's objection, many advocate delay, education, support, and negotiation in such cases [2,4,104,105]. The potential for organ donation offers comfort to the bereaved and should be offered to families, but it should not be the impetus for the diagnosis of brain death.

SUMMARY AND RECOMMENDATIONS

Brain death is the complete and irreversible loss of cerebral and brainstem function. In most countries and most situations, brain death is considered to be equivalent to cardiopulmonary death.

- The diagnosis of brain death is usually made by neurologic examination, provided certain prerequisites are met: the underlying cause is understood; the etiology is capable of producing neuronal death; and confounding from drug intoxication or poisoning, metabolic derangements, and hypothermia have been ruled out. (See 'Clinical setting' above.)

- The neurologic examination must demonstrate coma, no brain-generated response to external stimuli, and absent brainstem reflexes. (See 'Neurologic examination' above.)

- An apnea test is performed in all patients meeting all other brain death criteria who are stable enough to undergo the test. (See 'Apnea test' above.)

- Ancillary tests are required when clinical criteria cannot be applied and to supplement the clinical examination in young children. Tests of brain blood flow, especially those of brain perfusion, are the most reliable "stand-alone" laboratory examinations when the clinical criteria cannot be applied. (See 'Ancillary tests' above and 'Brain death in children' above.)

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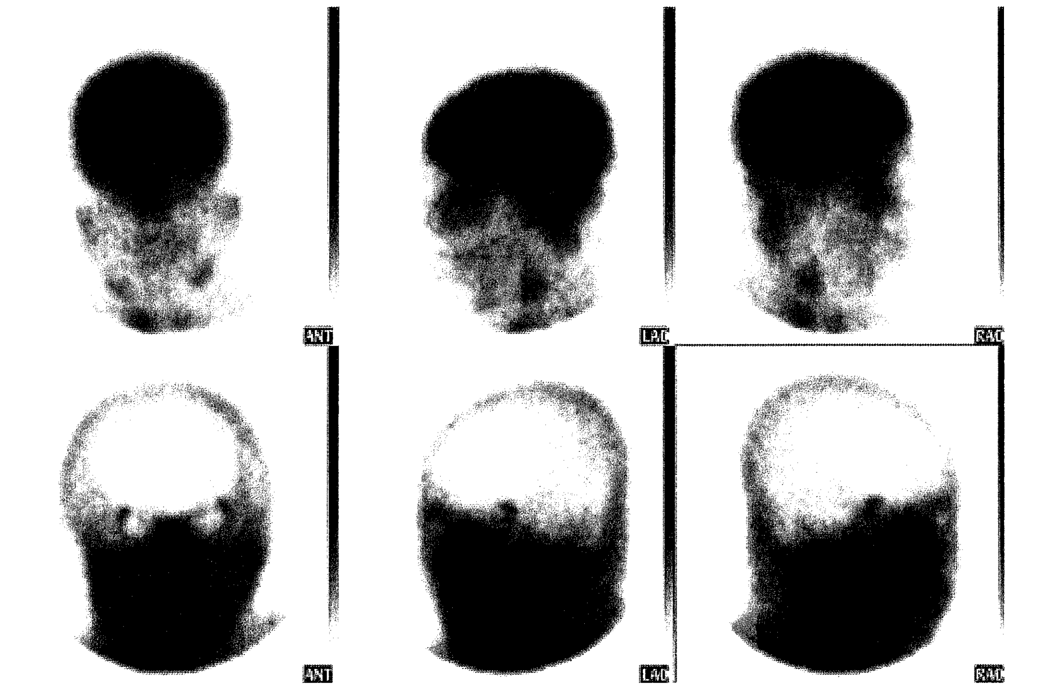
Topic 4831 Version 17.0

GRAPHICS

HMPAO-Tc99m SPECT in brain death



99mTc-labeled hexamethylpropyleneamineoxime (HMPAO), and subsequent imaging with single photon emission computed tomographic (SPECT) brain scintigraphy.
The top figures show anterior posterior and lateral views of a normal scan with uptake in the brain. The bottom figures (same sequence) show lack of brain perfusion and the "empty light bulb" and "hot nose" signs.

Courtesy of G Bryan Young, MD.

Graphic 76427 Version 4.0