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Brain Death Determination

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Abstract

In the United States, each year 1% to 2% of deaths are brain deaths. Considerable variation in the practice of determining brain death still remains, despite the publication of practice parameters in 1995 and an evidence-based guideline update in 2010. This review is intended to give bedside clinicians an overview of definition, the causes and pitfalls of misdiagnosing brain death, and a focus on the specifics of the brain death determination process.

Keywords

brain death, irreversible brain injury, absent brain stem reflexes, apnea test

Definition

The Uniform Determination of Death Act (UDDA) of 1980 proposed a legal definition of death, which has since been widely accepted. The act reads: "An individual who has sustained either irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all functions of the entire brain, including the brain stem, is dead."

Death, therefore, is a result of either a cardiopulmonary arrest with irreversible cessation of respiration and circulation, or it is a result of irreversible loss of all functions of the brain, including the brain stem. The latter is defined as Brain Death. A patient determined to be brain dead is clinically and legally dead.

Historical Perspective

One of the earlier references to brain death was made in an article by Horsley titled "On the Mode of Death in Cerebral Compression, and its Prevention" which appeared in *The Quarterly Medical Journal* in 1894—*"I wish in the following note to draw renewed attention to a clinical fact well known to and understood by some, but the general and vital importance of which seems to be hardly universally appreciated. I refer to the fact that cases of cerebral haemorrhage, of cerebral tumours, and of depressed fracture, as well as cases of sudden and violent concussions, especially when applied in the occipital region, die from failure of respiration, and not as is so often surmised, from failure of the heart."*

The concept of brain death and its determination remained unclear for almost a century. During that time, many important discoveries were made describing states of irreversible coma after severe brain injury, and more importantly, advances in life-sustaining therapies were used to keep patients with irreversible coma after severe brain injury "alive" for extended periods of time.[1] 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. In their opening statement they wrote: "Our primary purpose is to define irreversible coma as a new criterion for death. There are 2 reasons why there is a need for a definition: 1—improvement in resuscitative and supportive measures have led to increased efforts to save those who are desperately injured. Sometimes these efforts have only a partial success so that the result is an individual whose heart continues to beat but whose brain is irreversibly damaged. The burden is great on patients who suffer permanent loss of intellect, on their families, on the hospitals, and on those in need of hospital beds already occupied by these comatose patients. 2—Obsolete criteria for the definition of death can lead to controversy in obtaining organs for transplantation."[2] The role of the brain stem as a key critical component of irreversible coma was described in 1971.[3] Based on all the evidence available, The Conference of Medical Royal Colleges and their Faculties in the United Kingdom 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.[4] This statement provided guidelines that included a refinement of apnea testing

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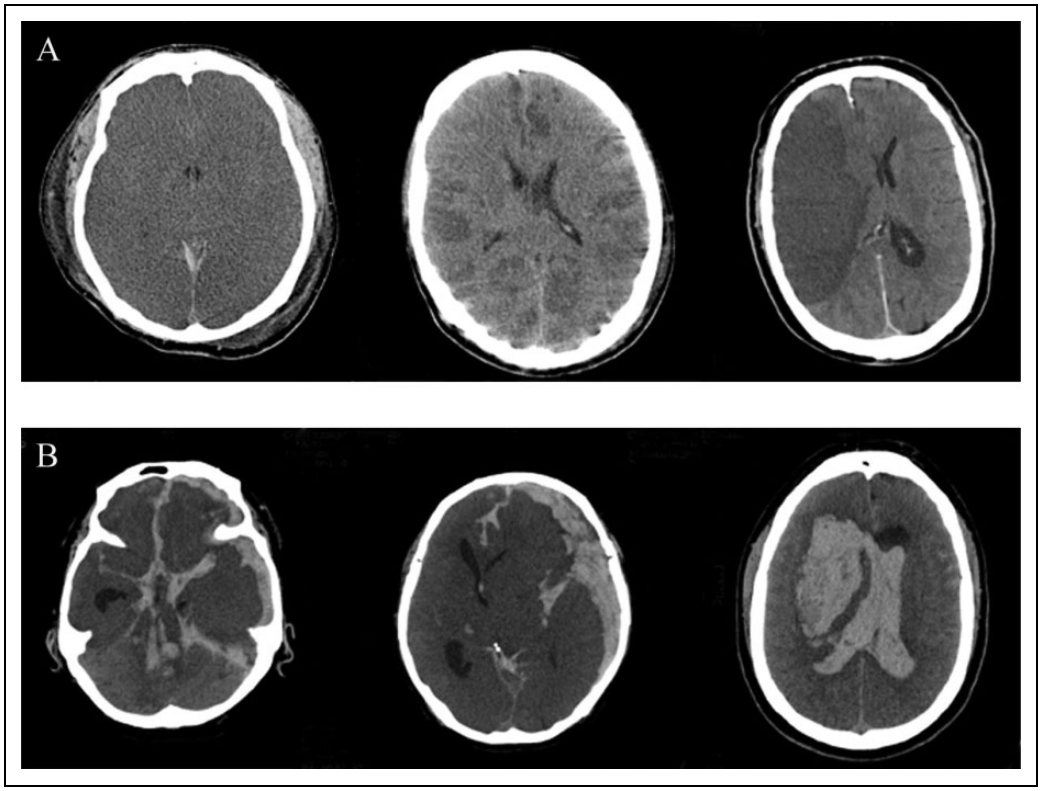

Figure 1. Ischemic (panel A) and hemorrhagic (panel B) brain injury resulting in brain death. Panel A—from left to right: diffuse cerebral edema; generalized swelling and extensive ischemia; and large right middle cerebral artery distribution ischemic stroke. Panel B—from left to right: acute subarachnoid and intraventricular hemorrhage with subdural hematoma; large left subdural hematoma with midline shift and diffuse brain edema; large right basal ganglia bleed with intraventricular extension, midline shift, and diffuse brain edema.

and pointed to the brain stem as the center of brain function: without it, no life exists.

The President's Commission report on "guidelines for the determination of death" resulted in the UDDA.[5] Since UDDA does not define "accepted medical standards", the American Academy of Neurology (AAN) published a 1995 practice parameter to delineate the medical standards for the determination of brain death.[6]

The parameter emphasized the 3 clinical findings necessary to confirm irreversible cessation of all functions of the entire brain, including the brain stem: coma (with a known cause), absence of brain stem reflexes, and apnea.

Despite publication of the practice parameters in 1995 and a subsequent evidence-based guideline update in 2010, considerable practice variation still remains.[7] The variability is not just among academic versus nonacademic hospital policies for determining brain death but between specialties within the same institution and even between the members of the same specialty practice group.[8,9]

Causes Leading to Brain Death

Brain injuries that eventually lead to brain death can be precipitated by extracranial or intracranial events. Intracranial causes are then divided into global versus localized and ischemic versus hemorrhagic (Figure 1). The main extracranial event causing brain death is a cardiopulmonary arrest followed by a delayed or inadequate cardiopulmonary resuscitation, causing prolonged and severe impairment of blood supply to the brain. The ensuing hypoxia and ischemia cause disturbance in cellular osmoregulation, which results in increased entry of water into brain parenchyma causing brain edema. Since the brain is encompassed by a rigid skull, this swelling will eventually cause blood flow disturbances and induce further hypoxia resulting in further edema. The detrimental consequence of this ongoing edema of the brain is an increase in intracranial pressure, which, if sufficiently high, will compress the entire brain and the brain stem and cause either herniation or complete cessation of cerebral circulation, causing aseptic necrosis of brain tissue and subsequently no blood uptake.[10]

The most common intracranial causes of brain death in adults are traumatic brain injury and subarachnoid hemorrhage,[11] while in children, abuse is reportedly more common than motor vehicle accidents or asphyxia.[12] The common mechanism of brain injury is manifested by an elevation in intracranial pressure to a point beyond the mean arterial pressure, resulting in cessation of cerebral blood flow leading to permanent cytotoxic injury of the intracranial neuronal tissue as described earlier.

The criteria for the diagnosis of brain death produced by the United Kingdom Medical Royal Colleges comprise a set of preconditions, which must be satisfied before formal tests for the absence of brain stem function may be performed.[4,13] These preconditions dictate that a clear cause of irremediable brain damage has been identified, and a set of necessary exclusions specifically ensure that reversible causes of brain stem depression such as depressant drugs, neuromuscular blocking agents, hypothermia, and metabolic imbalance have been excluded. Clinicians therefore must be aware of the pitfalls of brain death misdiagnosis in patients with conditions that might mimic brain stem death. The most common conditions on that list are locked-in syndrome and acute severe inflammatory polyneuropathies that can present as locked-in syndrome, hypothermia, and drug intoxications.

Mimics of Brain Death

Locked-In Syndrome

In 1966, Plum and Posner[14] introduced the term ''locked-in syndrome'' to refer to a neurological condition associated with infarction of the ventral pons commonly resulting from an infarct, hemorrhage, or trauma. The condition is most often caused by an acute embolus to the basilar artery.[15] The syndrome was described as quadriplegia, lower cranial nerve paralysis, and mutism with preservation of only vertical gaze and upper eyelid movement. It was redefined in 1986 as quadriplegia and anarthria with preservation of consciousness.[16] This redefinition served to clarify that mutism could imply unwillingness to speak.[17] Consciousness remains intact, and the patient is able to communicate intelligibly using eye blinking. The patient with ''locked-in'' syndrome is literally locked inside his body, aware of his environment but with a severely limited ability to interact with it. Consciousness persists because the tegmentum, with the reticular formation, is not affected.

Three varieties of ''locked-in syndrome,'' which are termed Classical, Incomplete, and Total, were proposed by Bauer in 1979.[18] The Classical variety is composed of patients with the signs and symptoms of ''locked-in syndrome'' as originally described by Plum and Posner. The Incomplete category is similar to the Classical variety except that the patients have remnants of voluntary motion besides upper eyelid and vertical eye movement. The Total variety is composed of a group of patients who are totally immobile and are unable to communicate. These patients are aware of both internal and external stimuli but are able to carry on only an internal monolog. Bauer further divided each variety into transient and chronic forms. When magnetic resonance imaging shows a ventral pontine insult in an otherwise unresponsive patient, the clinician should reexamine vertical eye movement. The diagnosis of locked-in syndrome can be missed if voluntary vertical eye movement is not assessed in patients who seem unresponsive.[19]

The Guillain-Barré syndrome, an acute severe inflammatory polyneuropathy, may present with a wide range of clinical pictures. Typically, there is a rapid onset of progressive, ascending paralysis with loss of deep tendon reflexes and usually some associated paresthesia. Many variants of this syndrome are recognized. Several sporadic reports have described the occurrence of an acute severe inflammatory polyneuropathy leading to a complete ''locked-in'' syndrome.[20-24] Misdiagnosis without a good antecedent history is potentially easy and carries disastrous consequences. This condition is reversible although undoubtedly associated with a significant morbidity.

Hypothermia

The most impressive confounder of brain death is hypothermia, whether it is accidental due to environmental exposure or therapeutically induced post-cardiac arrest. Hypothermia is defined as a body temperature less than 35°C and it is divided into 3 stages: mild hypothermia, when the body temperature is between 35°C and 32°C, moderate hypothermia when the body temperature is between 32°C and 30°C, and deep hypothermia when the body temperature is less than 30°C.[25] Hypothermia causes a downward spiral of loss of brain stem reflexes and pupillary dilatation and also delays drug metabolism, making the neurological assessment of brain death problematic. The response to light is lost at core temperatures of 28°C to 32°C, and brain stem reflexes disappear when the core temperature drops below 28°C.[26] These deficits are all potentially reversible, even after extreme hypothermia.[27]

Therapeutic hypothermia post-cardiac arrest has become a standard of care for its neuroprotective effect. The mechanisms for a possible neuroprotective effect of hypothermia are largely unknown. Among the mechanisms suggested to be influenced by hypothermia are free radical production and damage to the blood–brain barrier.[28] It is also postulated that hypothermia decreases metabolic rate and may thereby decrease lactic acidosis in the ischemic penumbra. Besides, hypothermia attenuates postischemic release of the excitotoxic neurotransmitters glutamic acid and aspartic acid, which are thought to cause exhaustion of surrounding postsynaptic neurons and delayed neuronal death.[29,30] This release of amino acids has recently been confirmed in a study of human stroke by Castillo et al.[31]

In therapeutic hypothermia as well as in accidental environmental exposure cases, the confounders are so significant that diagnosis of brain death should not even be attempted. Therefore, the AAN guidelines clearly stipulates to exclude confounders and even specifically mentions the dangers of assessing patients with hypothermia after cardiopulmonary resuscitation.[7] The clinical evaluation must include normalization of core temperature prior to neurologic assessment.

Drug Intoxication

The determination of brain death in a patient in overdose of coma requires exceptional vigilance on the part of the physician, since a variety of drugs and/or their metabolites including narcotics, benzodiazepines, tricyclic antidepressants, anticholinergics,

Table 1. Pharmacokinetic Characteristics of Selected CNS-Depressant Drugs.

Medication	Primary Route of Elimination	Half-Life	Comments
Fentanyl	Hepatic: 75%	3-12 hours	Prolonged elimination reported with decreased creatinine clearance, hepatic insufficiency, in elderly individuals, and in therapeutic hypothermia.[35,36]
Morphine	Hepatic: 90%	2-3 hours	Prolonged elimination reported with renal and hepatic insufficiency, with hypothermia[36], as well as in combination with sedatives.[37]
Propofol	Hepatic: 90%	0.5-1 hour	Terminal half-life after 10-day infusion is 1-3 days.[37]
Dexmedetomidine	Hepatic: 95%	2-2.67 hours	Clearance decreased in patients with hepatic impairment.[37]
Midazolam	Hepatic: 63%-80%	1.8-6.4 hours	Prolonged elimination is reported with hypothermia[36], as well as with renal insufficiency, in elderly individuals, patients with CHF, obesity.[37]
Vecuronium	Bile: 30%-50%, renal: 3%-35%, hepatic: 15%	0.85-1.3 hours	Prolonged elimination reported with hypothermia.[36]
Phenytoin	Hepatic: extensive	7-42 hours	Prolonged elimination reported with hypothermia.[36]
Phenobarbital	Hepatic	2-7 days	Prolonged elimination reported with hypothermia.[36]
Keppra	Renal: 66%, hepatic: minimal	6-8 hours	Prolonged elimination reported with decreased creatinine clearance, hepatic insufficiency, in elderly individuals.[37]

Abbreviations: CNS, central nervous system; CHF, congestive heart failure.

and barbiturates can closely mimic brain death. Ingested in large quantities, they can cause a partial loss of brain stem reflexes, but the pupillary response to light remains intact. 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.[32-34]

This is the reason why the AAN guidelines recommend excluding the presence of a central nervous system (CNS)-depressant drug effect by history, drug screen, and calculation of clearance using 5 times the drug's half-life (assuming normal hepatic and renal function), or, if available, drug plasma levels below the therapeutic range.[7] 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 4 times the elimination half-life of the substance, provided that the elimination of the drug is not interfered with by other drugs, organ dysfunction, or hypothermia. A quick reference of elimination paths and half-lives of commonly used CNS-depressant medications is provided in Table 1.[38] 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.[39]

Brain Death Declaration process: *Adults*

Although there is a universal acceptance of the concept of brain death, the survey of 80 countries by Wijdicks demonstrated major differences in the procedures for diagnosing brain death in adults.[40] Differences between these countries were found in the presence of legal standards on organ transplantation and practice guidelines for determination of brain death for adults, in the time of observation and required expertise of examining physicians, and on the number of physician required to declare brain death. Interestingly, in the United States, these differences can also be found between states and even different health care institutions. For example, although most states recognize whole brain death as the governing definition of death, the UDDA in the United States has been enacted only by 36 states and the District of Columbia. The remaining US states have comparable statutes but differences are notable. Virginia specifically calls for a specialist in the neurosciences.[41] Florida mandates 2 physicians; 1 must be the treating physician and the other must be a board-eligible or board-certified neurologist, neurosurgeon, internist, pediatrician, surgeon, or anesthesiologist.[42] In addition, New York and New Jersey have changed their statutes to accommodate religious objections.[43,44] These amendments require physicians to honor these requests and to continue medical care despite evidence of loss of brain function. One physician determination is sufficient in most states, but statutes in California, Alabama, Iowa, Louisiana, Florida, Virginia, Kentucky, and Connecticut require independent confirmation by another physician. In Alaska and Georgia, a registered nurse is delegated authority to declare death according to the statutory criteria but with subsequent certification by a physician within 24 hours. In Virginia, there is limited authority given to a registered nurse.[45]

Despite all these differences, the consensus remains that brain death is declared when brain stem reflexes, motor responses, and respiratory drive are absent in a normothermic, nondrugged patient in coma with a known irreversible massive brain lesion and no contributing metabolic derangements. In other words, the declaration of brain death is based on straightforward principles: the presence of unresponsive coma, the absence of brain stem reflexes, and the absence of respiratory drive after a CO_2 challenge. The American Academy of Neurology 1995 practice parameters emphasized these 3 clinical findings.[6] These recommendations were further validated in

the AAN 2010 update on guidelines to determine brain death in adults.[7] Despite these 2 publications, considerable practice variation still remains. In leading US hospitals, variations were found in prerequisites, the lowest acceptable core temperature, and the number of required examinations, among others.[8,9]

The following practical guidance for determination of brain death is based on 2010 AAN recommendations and is opinion based.[7] It is intended as a useful tool and a reminder that the brain death determination is a stepwise process, which must include the following 4 steps—preclinical testing, clinical examination, apnea testing, and ancillary testing.

Preclinical Testing

1. Establish irreversible coma and proximate cause of that coma: Exclude the presence of a CNS-depressant drug effect by history, drug screen, calculation of clearance using 5 times the drug's half-life (assuming normal hepatic and renal function), or, if available, drug plasma levels below the therapeutic range. Prior use of hypothermia (eg, after cardiopulmonary resuscitation for cardiac arrest) may delay drug metabolism. The legal alcohol limit for driving (blood alcohol content 0.08%) is a practical threshold below which an examination to determine brain death could reasonably proceed.

There should be no recent administration or continued presence of neuromuscular blocking agents (this can be defined by the presence of a train of 4 twitches with maximal ulnar nerve stimulation). There should be no severe electrolyte, acid-base, or endocrine disturbance (defined by severe acidosis or laboratory values markedly deviated from the norm).

2. Achieve normal core temperature: In most patients, a warming blanket is needed to raise the body temperature and maintain a normal or near-normal temperature (>36°C). After the initial equilibration of arterial CO_2 with mixed central venous CO_2, the PCO_2 rises steeply, but then more slowly when the body metabolism raises P_{CO_2}. To avoid delaying an increase in P_{CO_2}, normal or near-normal core temperature is preferred during the apnea test.
3. Achieve normal systolic blood pressure: Hypotension from loss of peripheral vascular tone or hypovolemia (diabetes insipidus) is common; vasopressors or vasopressin is often required. Neurologic examination is usually reliable with a systolic blood pressure $\geq$100 mm Hg.

Clinical Examination (Neurologic Assessment)

1. Coma: Patients must lack all evidence of responsiveness. Eye opening or eye movement to noxious stimuli is absent. Noxious stimuli should not produce a motor response other than spinally-mediated reflexes. Spinal reflex movements have been observed anyway from 13% to 79% of the brain-dead patients.[46,47] Spinal reflexes can be present at the time brain death is established or they can reappear afterwards.[46] Lazarus sign, a brief attempt of the body to flex at the waist, making it seem to rise, is the most dramatic and complex movement seen in patients with brain death. It is not very common and can be observed during an apnea test, an oculocephalic test, after a painful stimulus, and after removal of a ventilator. The other reflex movements observed are finger and toe jerks, extension at arms and shoulders, flexion of arms and feet, a slow turning of the head to one side, facial twitching, a persistent Babinski reflex, and tendon, abdominal, and cremasteric reflexes. An awareness of spinal reflexes may prevent delays in and misinterpretations of the brain-death diagnosis for both the physicians and the family.[39,47]
2. Absence of brain stem reflexes: *Absence of pupillary* response to a bright light is documented in both the eyes. Usually the pupils are fixed in a midsize or dilated position (4-9 mm). Constricted pupils suggest the possibility of drug intoxication. When uncertainty exists, a magnifying glass should be used.

Absence of ocular movements using oculocephalic testing and oculovestibular reflex testing. Once the integrity of the cervical spine is ensured, the head is briskly rotated horizontally and vertically. There should be no movement of the eyes relative to head movement. The oculovestibular reflex is tested by irrigating each ear with ice water (caloric testing) after the patency of the external auditory canal is confirmed. The head is elevated to 30°. Each external auditory canal is irrigated (1 ear at a time) with approximately 50 mL of ice water. Movement of the eyes should be absent during 1 minute of observation. Both sides are tested with an interval of several minutes. Cold caloric test takes the place of classical oculocephalic testing in suspected or known C-spine injury.

Absent corneal reflex is demonstrated by touching the cornea with a piece of tissue paper, a cotton swab, or squirts of water. No eyelid movement should be seen.

Absence of facial muscle movement to a noxious stimulus. Deep pressure on the condyles at the level of the temporomandibular joints and deep pressure at the supraorbital ridge should produce no grimacing or facial muscle movement.

Absence of the pharyngeal and tracheal reflexes. The pharyngeal or gag reflex is tested after stimulation of the posterior pharynx with a tongue blade or suction device. The tracheal reflex is most reliably tested by examining the cough response to tracheal suctioning. The catheter should be inserted into the trachea and advanced to the level of the carina followed by 1 or 2 suctioning passes.

Apnea Testing

Absence of a breathing drive is tested with a CO_2 challenge. Documentation of an increase in P_{CO_2} above normal levels is typical practice. It requires preparation before the test.

Prerequisites: (1) normotension, (2) normothermia, (3) euvolemia, (4) eucapnia (P_{CO_2} 35-45 mm Hg), (5) absence of hypoxia, and (6) no prior evidence of CO_2 retention (ie, chronic obstructive pulmonary disease and severe obesity).

Procedure:

- Adjust vasopressors to a systolic blood pressure $\geq$100 mm Hg.
- Preoxygenate for at least 10 minutes with 100% oxygen.
- If pulse oximetry oxygen saturation remains >95%, obtain a baseline blood gas (pH, P_{CO_2}, PaO_2).
- Disconnect the patient from the ventilator.
- Preserve oxygenation—for example, place an insufflation catheter through the endotracheal tube and close to the level of the carina and deliver 100% O_2 at 6 L/min. The flow of oxygen above 6 L/min may cause excessive CO_2 washout.
- Look closely for respiratory movements for 8 to 10 minutes. Respiration is defined as abdominal or chest excursions and may include a brief gasp.
- Abort if systolic blood pressure decreases to <90 mm Hg.
- Abort if oxygen saturation measured by pulse oximetry is <85% for >30 seconds. Retry procedure with continuous positive airway pressure 10 cm H_2O, or T-piece and 100% O_2 at 12 L/min.
- If no respiratory drive is observed, repeat blood gas (pH, P_{CO_2}, and P_{O_2}) after 10 minutes.
- If respiratory movements are absent, and arterial P_{CO_2} is $\geq$60 mm Hg and/or 20 mm Hg increase in arterial P_{CO_2} over a known baseline normal arterial P_{CO_2}, the apnea test result is positive (ie, supports the clinical diagnosis of brain death). The increase in the partial pressure of carbon dioxide occurs at a rate of approximately 3 mm Hg per minute.
- If the test is inconclusive but the patient is hemodynamically stable during the procedure, it may be repeated for a longer period of time (10-15 minutes) after the patient is again adequately preoxygenated.

Sleep apnea or severe pulmonary disease resulting in chronic retention of CO_2 may interfere with the clinical diagnosis of brain death, so that the diagnosis cannot be made with certainty on clinical grounds alone[10], unless the normal baseline P_{CO_2} is known for the patient. In that case, use the patient's baseline normal P_{CO_2} at the start of the apnea testing, and if the P_{CO_2} increases by 20 mm Hg or more from that baseline, the apnea test result supports the clinical diagnosis of brain death. In such cases, confirmatory tests are recommended.

The real challenge occurs in determining brain death in patients who are sustained on extracorporeal membrane oxygenation device. To assess brain death in these patients, apnea test can be performed without compromising oxygenation by decreasing (but not stopping) the sweep gas flow and increasing oxygen delivery through the membrane.[48,49]

Ancillary Tests

The determination of brain death is based on a comprehensive clinical assessment. In clinical practice, electroencephalography (EEG), cerebral angiography, nuclear scan, transcranial Doppler (TCD), computer tomography (CT) angiography (CTA), and magnetic resonance imaging/magnetic resonance angiogram are ancillary tests currently used in adults. They are divided into those that test the brain's electrical function and those that test cerebral blood flow. The preferred and commonly used tests are an EEG, nuclear scan, or cerebral angiogram. These confirmatory tests are not mandatory in the United States and can be used when uncertainty exists about the reliability of parts of the neurologic examination or when the apnea test cannot be performed.[7] A comprehensive clinical examination, when performed by skilled examiner, should have diagnostic accuracy.[50]

Electroencephalography. The American Clinical Neurophysiology Society has defined brain death as electrocerebral inactivity or electrocerebral silence. It is defined as no EEG activity over 2 μV when recording from scalp electrode pairs 10 or more cm apart with interelectrode impedances under 10 000 Ohms (10 KOhms) but over 100 Ohms.[51] In summary, the Society recommends adherence to the following guidelines in suspected cases of brain death:

- A minimum of 8 scalp electrodes should be used.
- Interelectrode impedance should be between 100 and 10,000 Ohms.
- 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 more than 1 Hz.
- Electroencephalography should demonstrate a lack of reactivity to intense somatosensory or audiovisual stimuli.

Nuclear Scan: Cerebral Scintigraphy. The Brain Imaging Council of the Society of Nuclear Medicine believes that agents such as diethylenetriaminepentaacetic acid, glucoheptonate, and pertechnetate (with perchlorate blockade) are much less favorable than 99mTc-labeled hexamethylpropyleneamineoxime and ethyl cysteinate dimer for assessment of cerebral perfusion.[52] Absence of uptake of isotope in brain parenchyma is supportive for a diagnosis of brain death. In summary, the Society recommends adherence to the following guidelines in suspected cases of brain death:

- The isotope should be injected within 30 minutes after its reconstitution.

Table 2. Age-Specific Diagnostic Criteria for Brain Death Declaration in Children.

Age	Clinical Assessment	Ancillary Testing	Observation Period
7 days to 2 months	2 examinations	2 EEGs	48 hours apart
	2 examinations	2 EEGs	24 hours apart
2 months to 1 year	1 examination	1 EEG showing ECS + angiogram showing no CBF	
More than 1 year	2 examinations	EEG and angiography optional	12 to 24 hours apart

Abbreviations: EEG, electroencephalogram; ECS, electrocerebral silence; CBF, cerebral blood flow.

- Anterior and both lateral planar image counts (500,000) of the head 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).
- No radionuclide localization in the middle cerebral artery, anterior cerebral artery, or basilar artery territories of the cerebral hemispheres (hollow skull phenomenon).
- No tracer in superior sagittal sinus (minimal tracer can come from the scalp).

Cerebral Angiography. Lack of cerebral circulation is an important confirmatory test for brain death. In cases of brain death, cerebral angiography usually demonstrates absent blood flow at or beyond the carotid bifurcation or Circle of Willis. The test must follow the following guidelines:

- The contrast medium should be injected in the aortic arch under high pressure and reach both anterior and posterior circulations.
- 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.

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.

Conventional 4-vessel cerebral angiography remains the ''gold standard'' imaging method, but CTA is emerging as an alternative.[53] Commonly, a 2-phase spiral CT protocol at 20 seconds and 60 seconds post injection of sufficient amount of contrast medium (120-150 mL) will show absence of arterial and venous opacification in brain death patients due to cessation of brain blood flow.[54] Further validation is still needed.

In adults, ancillary tests are not needed for the clinical diagnosis of brain death and cannot replace a neurologic examination. Physicians ordering ancillary tests should appreciate the disparities between tests and the potential for false-positives (ie, the test suggests brain death but the patient does not meet clinical criteria). Rather than ordering ancillary tests, physicians may decide not to proceed with the declaration of brain death if clinical findings are unreliable.

It is recommended that hospitals develop brain death policies and design a standard approach to declare brain death. Appendix A gives an example of a brain death declaration form from one of the teaching hospitals in California. Time of death is the time the arterial P_{CO_2} reached the target value. In patients with an aborted apnea test, the time of death is when the ancillary test has been officially interpreted.

Transcranial Doppler. Transcranial doppler (TCD) is a very sensitive and safe method for diagnosing cerebral circulatory arrest that may be used as a confirmatory test alongside EEG and angiography. Transcranial doppler evaluation of a brain death patient yields a ''reverberating or oscillating'' pattern of flow (normal arterial blood flow in systole and reversed flow in diastole secondary to the very high distal brain resistant in the brain-dead patients) leading to absence of net flow per unit of time. The reverberating pattern may progress to ''no flow'' in the advanced stages of brain death.[55] Transcranial doppler is more widely applicable than EEG and may be used earlier and safer than angiography.[56]

Brain Death in Children

The most common causes of brain death in children are trauma, anoxic encephalopathy, infections, and cerebral neoplasms. Although the definition of brain death and the declaration process in children is very similar to adult patients, there are several specific recommendations made by the American Academy of Pediatrics in 2011 and are outlined subsequently.[57]

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

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 (37 weeks gestational age) 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 preferably 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. 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.

In addition, age-related observation periods and specific neurodiagnostic tests were recommended for children younger than 1 year (Table 2). For children older than 1 year, the task force determined that the diagnosis of brain death could be made solely on a clinical basis and that laboratory studies were optional.

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.[58] Some believe that a diagnosis of brain death cannot be made reliably in very young infants. Committees in several countries decided to declare brain death only in children $\geq$2 months of age.

Recommendations from a Canadian forum published in 2006 had somewhat different qualifications regarding the brain death criteria for children.[59]

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 $\geq$36°C. Ancillary tests are required for presence of confounders or inability to establish clinical criteria.

For infants 30 days to 1 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 1 year, a second examiner should confirm the diagnosis as required by law if organ donation is planned. No time interval is required.

Although brain death cases comprise only 1% to 2% of all the deaths in the United States each year, many clinicians are still uncomfortable with the brain death determination process. Moreover, brain death patients form the majority of organ donors, bringing yet another level of complexity to be considered by the bedside clinician—timely declaration and continued resuscitation of the potential donor who is brain-dead and clear barriers between the treating physicians and the local Organ Procurement Organization (OPO). In the United States, OPOs must be informed ahead of time regarding the on-going brain death determination process but cannot make family contact until the brain death declaration process is completed. Laws and regulations differ from state to state, country to country but the important fact remains that the physicians involved in the brain death determination must not be connected to or work for the organ procurement company or be a part of the organ recovery team to eliminate any doubt of secondary gain.

Appendix A.

Declaration of Brain Death

Adults.

Declaration of Brain Death must be determined and recorded independently by:

1. Two Licensed physicians.
2. These physicians may not participate in the procedures for removing or transplanting a body part from the deceased.

Two separate physicians must complete Section I, *Mandatory Clinical Criteria.*

I. MANDATORY CLINICAL CRITERIA					
Vital Signs including Temperature, Blood Pressure, and Oxygen Saturation must be recorded in the chart at time of each declaration	First MD Exam		Second MD Exam		**Comments (required for all "NO" responses**
Initial Evaluation Absence of Reversible Causes	Yes	No	Yes	NO	
Injury Mechanism/Diagnosis consistent with Brain Death (*List in comments)	☐	☐	☐	☐	*1st Physician: *2nd Physician:
Primary Hypothermia excluded as the cause of coma **(core temp must be greater than 36.5°)**	☐	☐	☐	☐	
Other causes of death excluded, for example: (*Toxins/drugs (No contributory abnormalities) Metabolic parameters (No contributory abnormalities)	☐	☐	☐	☐	*Urine toxicology results:
Clinical Neurologic Examination					
Coma	☐	☐	☐	☐	
Pupils fixed and dilated	☐	☐	☐	☐	
Corneal reflex absent	☐	☐	☐	☐	
Oculocephalic reflex absent (patient not in C-Spine precautions)	☐	☐	☐	☐	
Oculovestibular reflex absent (pt in C-Spine precautions)	☐	☐	☐	☐	
Motor response to noxious central pain stimulation absent	☐	☐	☐	☐	
Gag / Cough reflex absent	☐	☐	☐	☐	
Absence of Spontaneous Respirations	☐	☐	☐	☐	
II. OPTIONAL CONFIRMATORY TESTING: After all clinical criteria are met; either an apnea or other confirmatory test can be used as an adjunct to the confirmation of clinical brain death. The addition of any confirmatory studies is at the discretion of the physician.					
Apnea Test (confirming absence of spontaneous respirations when):					
pH lesser than 7.30 **AND EITHER**	☐	☐	☐	☐	
PCO2 greater than 60 mm Hg **OR** greater than or equal to 20 mm Hg over baseline	☐	☐	☐	☐	
Other Confirmatory Tests					
EEG	☐	☐	☐	☐	
Nuclear scan	☐	☐	☐	☐	
Other:	☐	☐	☐	☐	
	☐	☐	☐	☐	

I certify that the above tests have been performed and that according to hospital policy ADM-XX-XXX this patient is brain dead.

1st Physician Name (Print)	**Physician Signature**	**Date**	**Time**
2nd Physician Name (Print)	**Physician Signature**	**Date**	**Time**

Instructions for Completion of Brain Death Declaration

Adults.

- Section I, Mandatory Clinical Criteria, must be performed and completed independently by each licensed physician signing the form.

Specific Information must be included in the Declaration:

Mandatory Clinical Criteria	
Injury Mechanism/ Diagnosis Consistent With Brain Death	A clear cause of irreversible brain damage has been identified, and reversible causes of brain stem depression such as depressant drugs, neuromuscular blocking agents, hypothermia and metabolic imbalance have been excluded. (Examples: Cerebral Infarct, Closed Head Injury, Encephalitis, Brain Tumor, Subarachnoid Hemorrhage . . .)
Vital Signs	**Temperature, Blood Pressure, and Oxygen Saturation** - Must be recorded in the chart/ flowsheet at the time of the Declaration and should not deviate from the norm.
Laboratory	A **Urine Toxicology Panel** is required for every patient who is declared Brain Dead. The results should be recorded in the chart at the time of Declaration. The physician believes that there is no significant metabolic abnormality that could be contributing to the findings on the neurologic exam listed below.
Clinical Neurologic Examination	**Pupils** – Fixed and dilated, nonreactive to light, **no corneal reflex.** **Gag** – Stimulate back of pharynx with tongue depressor/tug on endotracheal tube (i.e. tracheal tug). Movement of uvula or gagging excludes brain death. **Oculocephalic Reflex** – should not be tested in patients in C-spine precautions (use cold caloric test instead). The *absence* of the doll's eye sign is detected by holding upper eyelids open and tilting head forward with rapid, gentle turning of the patient's head from side to side. The eyes remain fixed in midposition, instead of the normal response of moving laterally toward the side opposite the direction the head is turned. **Oculovestibular Reflex – (Cold Caloric Test)** Indicated for patients in C-spine precautions. Irrigate ear canals with at least 60 mls and up to 100 mls ice water (caloric reflex). Any eye movement excludes brain death. Motor Response noxious stimulation – There must be no movement to deep central pain (except spinal reflexes). There must be no response to stimulation. **Absence of Spontaneous Respirations** - Observation *After all clinical criteria are met; other confirmatory tests can be used as adjunct(s) to the confirmation of clinical brain death. The addition of any confirmatory studies is at the discretion of the physician.
OPTIONAL CONFIRMATORY TESTING THE SECOND EXAM CAN REFER TO THE APNEA OR OTHER CONFIRMATORY TEST(S) OF THE FIRST EXAM	
Apnea Testing	Establish PCO2 between 35-45 mmHg prior to Apnea Test. Pre-oxygenate with 100% oxygen for 10 minutes. Obtain ABG. Disconnect patient from ventilator and administer passive 0_2 at 100% for at least 10 minutes, *if possible. Obtain ABG 10 minutes after disconnection to verify PCO2 of 60 mmHg or 20 mmHg greater than baseline. **If hypotension or arrhythmias occur during above procedures, return patient immediately to ventilator.* Record in the chart.
Signature	The physician's signature indicates that he or she has personally verified that all of the tests checked have been performed either by, or in the presence of, the physician. It indicates that all of the supporting vital signs, laboratory, and other clinical data on which the physician made the Declaration was in the chart at the time the Declaration was made.

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