Evidence-based guideline update: Determining brain death in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology

Eelco F.M. Wijdicks, Panayiotis N. Varelas, Gary S. Gronseth and David M. Greer

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SPECIAL ARTICLE

Evidence-based guideline update: Determining brain death in adults

Report of the Quality Standards Subcommittee of the American Academy of Neurology

Eelco F.M. Wijdicks, MD, PhD
Panayiotis N. Varelas, MD, PhD
Gary S. Gronseth, MD
David M. Greer, MD, MA

Address correspondence and reprint requests to the American Academy of Neurology, 1080 Montreal Avenue, St. Paul, MN 55116
guidelines@aan.com

ABSTRACT

Objective: To provide an update of the 1995 American Academy of Neurology guideline with regard to the following questions: Are there patients who fulfill the clinical criteria of brain death who recover neurologic function? What is an adequate observation period to ensure that cessation of neurologic function is permanent? Are complex motor movements that falsely suggest retained brain function sometimes observed in brain death? What is the comparative safety of techniques for determining apnea? Are there new ancillary tests that accurately identify patients with brain death?

Methods: A systematic literature search was conducted and included a review of MEDLINE and EMBASE from January 1996 to May 2009. Studies were limited to adults (aged 18 years and older).

Results and recommendations: In adults, there are no published reports of recovery of neurologic function after a diagnosis of brain death using the criteria reviewed in the 1995 American Academy of Neurology practice parameter. Complex-spontaneous motor movements and false-positive triggering of the ventilator may occur in patients who are brain dead. There is insufficient evidence to determine the minimally acceptable observation period to ensure that neurologic functions have ceased irreversibly. Apneic oxygenation diffusion to determine apnea is safe, but there is insufficient evidence to determine the comparative safety of techniques used for apnea testing. There is insufficient evidence to determine if newer ancillary tests accurately confirm the cessation of function of the entire brain. ***Neurology*® 2010;74:1911–1918**

GLOSSARY

AAN = American Academy of Neurology; **CI** = confidence interval; **CPAP** = continuous positive airway pressure; **CTA** = CT angiography; **HMPAO** = Tc 99mHexametazime; **MRA** = magnetic resonance angiography; **PEEP** = positive end-expiratory pressure; **SSEP** = somatosensory evoked potential; **TCD** = transcranial Doppler; **UDDA** = Uniform Determination of Death Act.

The President's Commission report on "guidelines for the determination of death"[1] culminated in a proposal for a legal definition that led to the Uniform Determination of Death Act (UDDA). The act reads as follows: "An individual who has sustained either 1) irreversible cessation of circulatory and respiratory functions, or 2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made with accepted medical standards."[2] Most US state laws have adopted the UDDA. Several states have added amendments regarding physician qualifications, confirmation by a second physician, or religious exemption.

The 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.[3] 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 brainstem reflexes, and apnea.

Despite publication of the practice parameter, considerable practice variation remains. In leading US hospitals, variations were found in prerequisites, the lowest acceptable core temperature, and the number of required examinations, among oth-

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From the Division of Critical Care Neurology (E.F.M.W.), Mayo Clinic, Rochester, MN; Department of Neurology (P.N.V.), Henry Ford Hospital, Detroit, MI; Department of Neurology (G.S.G.), University of Kansas Medical Center, Kansas City; and Department of Neurology (D.M.G.), Massachusetts General Hospital, Boston.

Appendices e-1–e-4 and references e1–e5 are available on the *Neurology*® Web site at www.neurology.org.

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ers.[4] Additionally, audits of charts of patients diagnosed with brain death show common deficiencies in documentation.[5]

This update sought to use evidence-based methods to answer 5 questions historically related to variations in brain death determination[4] to promote uniformity in diagnosis:

1. Are there patients who fulfill the clinical criteria of brain death who recover brain function?
2. What is an adequate observation period to ensure that cessation of neurologic function is permanent?
3. Are complex motor movements that falsely suggest retained brain function sometimes observed in brain death?
4. What is the comparative safety of techniques for determining apnea?
5. Are there new ancillary tests that accurately identify patients with brain death?

DESCRIPTION OF THE ANALYTIC PROCESS A literature search was conducted of MEDLINE and EMBASE from January 1996 to May 2009. Search terms included the MeSH term "brain death" and the text words "brain death," "irreversible coma," and "apnea test." Studies were limited to those involving adults (aged 18 years and older) and those in English.

Articles were included if they contained evidence relevant to one of the questions. We excluded articles that confirmed prior observations, review articles, bioethical reviews, articles without description of a brain death examination, articles with questionable practices (e.g., using laboratory tests in patients treated with sedative drugs), and articles describing infrequently used ancillary technology (e.g., jugular venous saturation).

Articles were independently rated by at least 2 panel members based on the AAN evidence classification system (appendix e-3 on the *Neurology*® Web site at www.neurology.org). Articles pertinent to questions 1, 2, 4, and 5 were rated using the diagnostic accuracy scheme. Articles pertinent to question 3 were rated using the screening scheme. Differences in rating were resolved by discussion. Recommendations were linked to the strength of the evidence (appendix e-4).

ANALYSIS OF EVIDENCE The search yielded 367 articles, and 38 met inclusion criteria.

Are there patients who fulfill the clinical criteria of brain death who recover brain function? Nine Class IV studies have been published on the recognition of brain-death mimics, including fulminant Guillain-Barré syndrome, organophosphate intoxication, high cervical spinal cord injury, lidocaine toxicity, baclofen overdose, and delayed vecuronium clearance.[6-14] The description of the examinations provided in these studies indicated that a complete brain death examination was not performed in any of these patients. We found no reports in peer-reviewed medical journals of recovery of brain function after a determination of brain death using the AAN practice parameter.

Conclusion. In adults, recovery of neurologic function has not been reported after the clinical diagnosis of brain death has been established using the criteria given in the 1995 AAN practice parameter.

What is an adequate observation period to ensure that cessation of neurologic function is permanent? Recommendations for the length of observation periods have varied extensively throughout the world and the United States.[5,15] There are no detailed studies on serial examinations in adult patients who have been declared brain dead.

Conclusion. There is insufficient evidence to determine the minimally acceptable observation period to ensure that neurologic functions have ceased irreversibly.

Are complex motor movements that falsely suggest retained brain function sometimes observed in brain death? Six Class III studies described spontaneous and reflex movements in patients meeting criteria for brain death. These included single reports of facial myokymia, transient bilateral finger tremor, repetitive leg movements, ocular microtremor, and cyclical constriction and dilatation in light-fixed pupils.[16-21] One Class III study of 144 patients pronounced brain dead found 55% (95% confidence interval [CI] 47–63) of patients had retained plantar reflexes, either flexion or "stimulation induced undulating toe flexion."[22] Another study documented plantar flexion and flexion synergy bilaterally that persisted for 32 hours after the determination of brain death.[23]

Two Class III studies suggested that the ventilator may sense small changes in tubing pressure and provide a breath that could suggest breathing effort by the patient where none exists.[24,25] This phenomenon is more common in current ventilators and in patients who have had chest tubes placed. Changes in transpleural pressure from the heartbeat may also trigger the ventilator. These studies suggest that the determination of apnea can be assessed reliably only by disconnecting the ventilator.[24,25]

Conclusion. For some patients diagnosed as brain dead, complex, non–brain-mediated spontaneous movements can falsely suggest retained brain function. Additionally, ventilator autocycling may falsely suggest patient-initiated breathing.

What is the comparative safety of techniques for determining apnea? There have been 4 published studies on the technique of apnea tests, none of which com-

pared 1 technique to another; thus, all were Class IV. One study used preoxygenation and an apneic oxygenation-diffusion technique in 212 patients.[26] In 16 patients (7%) apnea testing was not attempted due to inability to maintain a stable blood pressure, high positive end expiratory pressure requirements, or refractory hypoxemia despite pretest oxygenation using 100% oxygen for 10 minutes. The apnea test was aborted in 3% of patients due to progressive hypotension or hypoxemia after ventilator disconnection.[26]

One study of 20 adults examined disconnection of the ventilator using a T-piece and continuous positive airway pressure (CPAP) valve (CPAP valve of 10 cm of water and oxygen administration at 12 L/min). Apnea testing could be completed in all patients with the additional use of a CPAP valve.[27]

Two studies have suggested monitoring of the apnea test with transcutaneous carbon dioxide partial pressure monitoring. However, comparison with predicting P_{CO_2} rise using an estimated 3 mm Hg increase per minute has not been performed. It is unclear whether this device reduces blood gas testing (and thus cost) during the apnea test.[28,29]

Conclusion. Apneic oxygenation diffusion to determine apnea is safe, but there is insufficient evidence to determine the comparative safety of techniques used for apnea testing.

Are there new ancillary tests that accurately identify patients with brain death? ***MRI and magnetic resonance angiography.*** One Class II[30] and 3 Class IV[31-33] studies examined MRI and magnetic resonance angiography (MRA). Two Class IV[31,32] case series of 19 patients meeting clinical and EEG criteria for brain death documented loss of flow voids in the cavernous portion of the carotid artery with MRA. In these studies, MRA attained a sensitivity for brain death by clinical and EEG criteria of 100% (95% CI 83%–100%). Because patients not meeting clinical criteria for brain death were not included in these studies, it was not possible to determine the false-positive rate of MRA for brain death from these Class IV studies.

A Class II[30] case-control study of 20 patients who were clinically diagnosed as brain dead also included 10 patients who were comatose but not brain dead. MRA revealed absent arterial flow in the intracerebral circulation only in patients diagnosed as brain dead (sensitivity 100%, 95% CI 84%–100%; specificity 100%, 95% CI 72.2%–100%).[30] This study lacked the statistical precision to confidently state that the false-positive rate of MRA was acceptably low (study consistent with a false-positive rate up to 27.8%).

CT angiography. Five Class IV studies[34-38] and 1 Class III study documented the results of CT angiography (CTA) in patients meeting clinical criteria for brain death. One case series showed intracranial opacification of blood vessels in 10 of 21 patients (48%; 95% CI 26%–69%) with isoelectric EEGs.[34] In another case series, 13 of 43 patients with absent opacification of intracranial blood vessels on cerebral angiography had CTA-demonstrated intracranial blood flow (30%; 95% CI 17%–43%).[35] A Class IV study[36] of 105 patients found residual opacified vessels on CTA in up to 56% of patients. A Class IV study of 27 patients found CTA evidence of opacification of intracranial vessels in 3 patients.[37] One case report documented preserved flow on transcranial Doppler (TCD) but no opacification of intracranial vessels in 1 patient.[38] These Class IV studies included only patients meeting criteria for brain death.

One Class III case-control study[39] included patients meeting criteria for brain death and normal controls. CTA demonstrated no flow in 14 patients diagnosed with brain death (sensitivity 100%, 95% CI 78.5%–100%). CTA demonstrated cerebral flow in all normal controls (false-positive rate 0%, 95% CI 0%–25.9%). This study did not include non-brain-dead comatose patients. Thus, the false-positive rate of CTA in patients with loss of most brainstem reflexes, but who are not brain dead, cannot be determined.

Somatosensory evoked potentials. Two Class III studies examined the use of nasopharyngeal electrode recording of somatosensory evoked potentials (SSEPs) to confirm brain death.[40,e1] One cohort survey of 181 comatose patients found disappearance of P14 (presumably generated in the medial lemniscus and cuneate nucleus) on nasopharyngeal electrode SSEP recordings in all 108 patients diagnosed with brain death by clinical criteria (sensitivity 100%, 95% CI 96.6%–100%). In comatose patients who were not brain dead, the P14 was never absent (specificity 100%, 95% CI 95%–100%).[40] In this study it was unclear if SSEPs were interpreted without knowledge of the patient's brain death status. A Class III cohort survey of 28 patients demonstrated similar findings.[e1] These studies suggest that P14 recordings using midfrontal scalp-nasopharyngeal montage could be a valuable confirmatory test. However, the technique has not been used on a routine basis and interobserver variability studies have not been performed.[40]

Bispectral index. One Class III study evaluated bispectral index monitoring in 54 patients and noted a gradual decline in bispectral index values to 0 in 9 patients, implicating isoelectric EEG. Bispectral index was compared with EEG in 24 patients and with TCD in 18 patients; no discrepancies were found.[e2]

The technology is rarely used in intensive care units and has not been compared to flow studies.

Conclusion. Because of a high risk of bias and inadequate statistical precision, there is insufficient evidence to determine if any new ancillary tests accurately identify brain death.

RECOMMENDATIONS

1. The criteria for the determination of brain death given in the 1995 AAN practice parameter have not been invalidated by published reports of neurologic recovery in patients who fulfill these criteria (Level U).
2. There is insufficient evidence to determine the minimally acceptable observation period to ensure that neurologic functions have ceased irreversibly (Level U).
3. Complex-spontaneous motor movements and false-positive triggering of the ventilator may occur in patients who are brain dead (Level C).
4. There is insufficient evidence to determine the comparative safety of techniques used for apnea testing (Level U).
5. There is insufficient evidence to determine if newer ancillary tests accurately confirm the cessation of function of the entire brain (Level U).

CLINICAL CONTEXT This review highlights severe limitations in the current evidence base. Indeed, there is only 1 study that prospectively derived criteria for the determination of brain death.[e3]

Despite the paucity of evidence, much of the framework necessary for the development of "accepted medical standards" for the declaration of brain death is based on straightforward principles. These principles can be derived from the definition of brain death provided by the UDDA. To determine "cessation of all functions of the entire brain, including the brain stem," physicians must determine the presence of unresponsive coma, the absence of brainstem reflexes, and the absence of respiratory drive after a CO_2 challenge. To ensure that the cessation of brain function is "irreversible," physicians must determine the cause of coma, exclude mimicking medical conditions, and observe the patient for a period of time to exclude the possibility of recovery.

The UDDA-derived principles define the essential elements needed to determine brain death. However, because of the deficiencies in the evidence base, clinicians must exercise considerable judgment when applying the criteria in specific circumstances.

RECOMMENDATIONS FOR FUTURE RESEARCH Future prospective studies of brain death determination are needed. Areas of future research include examining the safety of the apnea test, seeking alternative methods of apnea testing, performing an audit of adequate documentation, and studying the competence of examiners. Details of the neurologic examination may be subjected to an expert panel review, possibly including international organizations.

PRACTICAL (NON-EVIDENCE-BASED) GUIDANCE FOR DETERMINATION OF BRAIN DEATH Many of the details of the clinical neurologic examination to determine brain death cannot be established by evidence-based methods. The detailed brain death evaluation protocol that follows is intended as a useful tool for clinicians. It must be emphasized that this guidance is opinion-based. Alternative protocols may be equally informative.

The determination of brain death can be considered to consist of 4 steps.

I. The clinical evaluation (prerequisites).
   A. Establish irreversible and proximate cause of coma.
      The cause of coma can usually be established by history, examination, neuroimaging, and laboratory tests.
      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 (e.g., 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).
   B. 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 $Paco_2$ rises steeply, but then more slowly when the body metabolism raises $Paco_2$.To avoid delaying an increase in

$PaCO_2$, normal or near-normal core temperature is preferred during the apnea test.

C. Achieve normal systolic blood pressure.
Hypotension from loss of peripheral vascular tone or hypovolemia (diabetes insipidus) is common; vasopressors or vasopressin are often required. Neurologic examination is usually reliable with a systolic blood pressure ≥100 mm Hg.

D. Perform 1 neurologic examination (sufficient to pronounce brain death in most US states).
If a certain period of time has passed since the onset of the brain insult to exclude the possibility of recovery (in practice, usually several hours), 1 neurologic examination should be sufficient to pronounce brain death. However, some US state statutes require 2 examinations.
Legally, all physicians are allowed to determine brain death in most US states. Neurologists, neurosurgeons, and intensive care specialists may have specialized expertise. It seems reasonable to require that all physicians making a determination of brain death be intimately familiar with brain death criteria and have demonstrated competence in this complex examination. Brain death statutes in the United States differ by state and institution. Some US state or hospital guidelines require the examiner to have certain expertise.

II. The clinical evaluation (neurologic assessment).

A. 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. The clinical differentiation of spinal responses from retained motor responses associated with brain activity requires expertise.

B. Absence of brainstem reflexes.

- Absence of pupillary response to a bright light is documented in both 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 degrees. 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.
- Absence of corneal reflex.
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.

C. Apnea.

- Absence of a breathing drive.
Absence of a breathing drive is tested with a CO_2 challenge. Documentation of an increase in $PaCO_2$ above normal levels is typical practice. It requires preparation before the test.
Prerequisites: 1) normotension, 2) normothermia, 3) euvolemia, 4) eucapnia ($PaCO_2$ 35–45 mm Hg), 5) absence of hypoxia, and 6) no prior evidence of CO_2 retention (i.e., chronic obstructive pulmonary disease, severe obesity).
Procedure:
  - Adjust vasopressors to a systolic blood pressure ≥100 mm Hg.

- Preoxygenate for at least 10 minutes with 100% oxygen to a Pa_{O_2} >200 mm Hg.
- Reduce ventilation frequency to 10 breaths per minute to eucapnia.
- Reduce positive end-expiratory pressure (PEEP) to 5 cm H_2O (oxygen desaturation with decreasing PEEP may suggest difficulty with apnea testing).
- If pulse oximetry oxygen saturation remains >95%, obtain a baseline blood gas (Pa_{O_2}, Pa_{CO_2}, pH, bicarbonate, base excess).
- Disconnect the patient from the ventilator.
- Preserve oxygenation (e.g., 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).
- Look closely for respiratory movements for 8–10 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 T-piece, CPAP 10 cm H_2O, and 100% O_2 12 L/min.
- If no respiratory drive is observed, repeat blood gas (Pa_{O_2}, Pa_{CO_2}, pH, bicarbonate, base excess) after approximately 8 minutes.
- If respiratory movements are absent and arterial P_{CO_2} is ≥60 mm Hg (or 20 mm Hg increase in arterial P_{CO_2} over a baseline normal arterial P_{CO_2}), the apnea test result is positive (i.e., supports the clinical diagnosis of brain death).
- 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.

III. Ancillary tests.

In clinical practice, EEG, cerebral angiography, nuclear scan, TCD, CTA, and MRI/MRA are currently used ancillary tests in adults (see appendix 1). Most hospitals will have the logistics in place to perform and interpret an EEG, nuclear scan, or cerebral angiogram, and these 3 tests may be considered the preferred tests. Ancillary tests can be used when uncertainty exists about the reliability of parts of the neurologic examination or when the apnea test cannot be performed. In some protocols, ancillary tests are used to shorten the duration of the observation period.

The interpretation of each of these tests requires expertise. 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 (i.e., 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.

IV. Documentation.

The time of brain death is documented in the medical records. 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. A checklist is filled out, signed, and dated (appendix 2). Federal and state law requires the physician to contact an organ procurement organization following determination of brain death.[e4,e5]

DISCLOSURE

Dr. Wijdicks serves as an editorial board member of *Clinical Neurology and Neurosurgery*, *The Neurologist, Liver Transplantation,* and *Journal of Clinical Neurology*, as a section editor of *Medical Reviews in Neurology* and *First Consult*, and as Editor-in-Chief of *Neurocritical Care*; and receives royalties from *The Comatose Patient* (2008), *Neurological Complications of Critical Illness* (2009), and *The Practice of Emergency and Critical Care Neurology* (2010) (all published by Oxford University Press). Dr. Varelas serves on a scientific advisory board for Gift of Life of Michigan; serves on the editorial board of *Neurocritical Care*; has received funding for travel from and serves on the speaker's bureau for The Medicines Company; receives royalties from the publication of *Seizures in the ICU* (Springer, 2004–2008); receives research support from Alsius Company and The Medicines Company; and holds stock in The Medicines Company. Dr. Gronseth serves as an editorial advisory board member of *Neurology Now*; serves on a speakers' bureau for Boehringer Ingelheim; and receives honoraria from Boehringer Ingelheim and the American Academy of Neurology. Dr. Greer receives royalties from publication of *Acute Ischemic Stroke: An Evidence-Based Approach* (Wiley and Sons, 2007); served on the speakers' bureau for Boehringer Ingelheim; received research support from Boehringer Ingelheim; and has served as a consultant in a medico-legal case.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and

the physician caring for the patient, based on all the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, *Neurology*® peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

APPENDIX 1

Methods of ancillary testing for the determination of brain death (see text for indications)

Cerebral angiography

- 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.

Electroencephalography

- A minimum of 8 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

- TCD is useful only if a reliable signal is found. The abnormalities should include either reverberating flow or 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. There should be bilateral insonation and anterior and posterior insonation. The probe should be placed at the temporal bone, above the zygomatic arch and the vertebrobasilar arteries, through the suboccipital transcranial window.
- Insonation through the orbital window can be considered to obtain a reliable signal. TCD may be less reliable in patients with a prior craniotomy.

Cerebral scintigraphy (technetium Tc 99m hexametazime(HMPAO)

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

APPENDIX 2

Checklist for determination of brain death

Prerequisites (all must be checked)

- □ Coma, irreversible and cause known
- □ Neuroimaging explains coma
- □ CNS depressant drug effect absent (if indicated toxicology screen; if barbiturates given, serum level < 10 μg/mL)
- □ No evidence of residual paralytics (electrical stimulation if paralytics used).
- □ Absence of severe acid-base, electrolyte, endocrine abnormality
- □ Normothermia or mild hypothermia (core temperature > 36°C)
- □ Systolic blood pressure ≥ 100 mm Hg
- □ No spontaneous respirations

Examination (all must be checked)

- □ Pupils nonreactive to bright light
- □ Corneal reflex absent
- □ Oculocephalic reflex absent (tested only if C-spine integrity ensured)
- □ Oculovestibular reflex absent
- □ No facial movement to noxious stimuli at supraorbital nerve, temporomandibular joint
- □ Gag reflex absent
- □ Cough reflex absent to tracheal suctioning
- □ Absence of motor response to noxious stimuli in all 4 limbs (spinally mediated reflexes are permissible)

Apnea testing (all must be checked)

- □ Patient is hemodynamically stable
- □ Ventilator adjusted to provide normocarbia ($PaCo_2$ 34–45 mm Hg)
- □ Patient preoxygenated with 100% FiO_2 for > 10 minutes to $PaO_2 > 200$ mm Hg
- □ Patient well-oxygenated with a PEEP of 5 cm of water
- □ Provide oxygen via a suction catheter to the level of the carina at 6 L/min or attach T-piece with CPAP at 10 cm H_2O
- □ Disconnect ventilator
- □ Spontaneous respirations absent
- □ Arterial blood gas drawn at 8–10 minutes, patient reconnected to ventilator
- □ $PCO_2 \geq 60$ mm Hg, or 20 mm Hg rise from normal baseline value

OR:

- □ Apnea test aborted

Ancillary testing (only 1 needs to be performed; to be ordered only if clinical examination cannot be fully performed due to patient factors, or if apnea testing inconclusive or aborted)

- □ Cerebral angiogram
- □ HMPAO SPECT
- □ EEG
- □ TCD

Time of death (DD/MM/YY) _____

Name of physician and signature _____

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REFERENCES

1. Guidelines for the determination of death: report of the medical consultants on the diagnosis of death to the President's commission for the study of ethical problems in medicine and biochemical and behavioral research. JAMA 1981;246:2184–2186.
2. Uniform Determination of Death Act, 12 uniform laws annotated 589 (West 1993 and West suppl 1997).
3. The Quality Standards Subcommittee of the American Academy of Neurology. Practice parameters for determining brain death in adults (summary statement). Neurology 1995;45:1012–1014.
4. Greer DM, Varelas PN, Haque S, Wijdicks EFM. Variability of brain death determination guidelines in leading US neurologic institutions. Neurology 2008;70:284–289.

5. Wang M, Wallace P, Gruen JP. Brain death documentation: analysis and issues. Neurosurgery 2002;51:731–736.
6. Ostermann ME, Young B, Sibbald WJ, Nicolle MW. Coma mimicking brain death following baclofen overdose. Intensive Care Med 2000;26:1144–1146.
7. Richard IH, LaPointe M, Wax P, Risher W. Non-barbiturate, drug-induced reversible loss of brainstem reflexes. Neurology 1998;51:639–640.
8. Waters CE, French G, Burt M. Difficulty in brainstem death testing in the presence of high spinal cord injury. Br J Anaesth 2004;92:760–764.
9. Peter JV, Prabhakar AT, Pichamuthu K. In-laws, insecticide- and a mimic of brain death. Lancet 2008;371:622.
10. Stojkovic T, Verdin M, Hurtevent JF, Laureau E, Krivosic-Horber R, Vermersch P. Guillain-Barré syndrome resembling brainstem death in a patient with brain injury. J Neurol 2001;248:430–432.
11. Rivas S, Douds GL, Ostdahl RH, Harbaugh KS. Fulminant Guillain-Barré syndrome after closed head injury: a potentially reversible cause of an ominous examination. J Neurosurg 2008;108:595–600.
12. Friedman Y, Lee L, Wherrett JR, Ashby P, Carpenter S. Simulation of brain death from fulminant de-efferentation. Can J Neurol Sci 2003;30:397–404.
13. Joshi MC, Azim A, Gupta GL, Poddar BP, Baronia AK, Singh RK. Guillain-Barré syndrome with absent brainstem reflexes: a report of two cases. Anaesth Intensive Care 2008;36:867–869.
14. Kainuma M, Miyake T, Kanno T. Extremely prolonged vecuronium clearance in a brain death case. Anesthesiology 2001;95:1023–1024.
15. Wijdicks EFM. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. Neurology 2002;58:20–25.
16. Saposnik G, Bueri JA, Maurino J, Saizar R, Garretto NS. Spontaneous and reflex movements in brain death. Neurology 2000;54:221–223.
17. Santamaria J, Orteu N, Iranzo A, Tolosa E. Eye opening in brain death. J Neurol 1999;246:720–722.
18. Araullo ML, Frank JI, Goldenberg FD, Rosengart AJ. Transient bilateral finger tremor after brain death. Neurology 2007;68:E22.
19. Jung KY, Han SG, Lee KH, Chung CS. Repetitive leg movements mimicking periodic leg movement during sleep in a brain-dead patient. Eur J Neurol 2006;13:e3–e4.
20. Bolger C, Bojanic S, Phillips J, Sheahan N, Coakley D, Malone J. Ocular microtremor in brain stem death. Neurosurgery 1999;44:1201–1206.
21. Shulgman D, Parulekar M, Elston JS, Farmery A. Abnormal pupillary activity in a brainstem-dead patient. Br J Anaesth 2001;86:717–720.
22. de Freitas GR, Andre C. Absence of the Babinski sign in brain death. J Neurol 2005;252:106–107.
23. Zubkov AY, Wijdicks EFM. Plantar flexion and flexion synergy in brain death. Neurology 2008;70:e74.
24. Wijdicks EFM, Manno EM, Holets SR. Ventilator self-cycling may falsely suggest patient effort during brain death determination. Neurology 2005;65:774.
25. Willatts SM, Drummond G. Brain death and ventilator trigger settings. Anaesthesia 2000;55:676–684.
26. Wijdicks EFM, Rabinstein AA, Manno EM, Atkinson JD. Pronouncing brain death: contemporary practice and safety of the apnea test. Neurology 2008;71:1240–1244.
27. Levesque S, Lessard MR, Nicole PC, et al. Efficacy of a T-piece system and a continuous positive airway pressure system for apnea testing in the diagnosis of brain death. Crit Care Med 2006;34:2213–2216.
28. Lang CJG, Heckmann JG, Erbguth F, et al. Transcutaneous and intra-arterial blood gas monitoring: a comparison during apnoea testing for the determination of brain death. Eur J Emerg Med 2002;9:51–56.
29. Vivien B, Marmion F, Roche S, et al. An evaluation of transcutaneous carbon dioxide partial pressure monitoring during apnea testing in brain-dead patients. Anesthesiology 2006;104:701–707.
30. Karantanas AH, Hadjigeorgiou GM, Paterakis K, Sfiras D, Komnos A. Contribution of MRI and MR angiography in early diagnosis of brain death. Eur Radiol 2002;12:2710–2716.
31. Ishii K, Onuma T, Kinoshita T, Shiina G, Kameyama M, Shimosegawa Y. Brain death: MR and MR angiography. AJNR Am J Neuroradiol 1996;17:731–735.
32. Matsumura A, Meguro K, Tsurushima H, et al. Magnetic resonance imaging of brain death. Neurol Med Chir 1996; 36:166–171.
33. Lovblad KO, Bassetti C. Diffusion-weighted magnetic resonance imaging in brain death. Stroke 2000;31:539–542.
34. Quesnel C, Fulgencio J-P, Adrie C, et al. Limitations of computed tomography in the diagnosis of brain death. Intensive Care Med 2007;33:2129–2135.
35. Combes JC, Chomel A, Ricolfi F, d'Athis P, Freysz M. Reliability of computed tomographic angiography in the diagnosis of brain death. Transplant Proc 2007;39:16–20.
36. Frampas E, Videcoq M, de Kerviler E, et al. CT angiography for brain death diagnosis. Am J Neuroradiol 2009;30:1566–1570.
37. Escudero D, Otero J, Marques L, et al. Diagnosing brain death by CT perfusion and multislice CT angiography. Neurocrit Care 2009;11:261–271.
38. Greer DM, Strozyk D, Schwamm LH. False positive CT angiography in brain death. Neurocrit Care 2009;11:272–275.
39. Dupas B, Gayet-Delacroix M, Villers D, Antonioli D, Veccherini MF, Soulillou JP. Diagnosis of brain death using two-phase spiral CT. Am J Neuroradiol 1998;19:641–647.
40. Wagner W. Scalp, earlobe and nasopharyngeal recordings of the median nerve somatosensory evoked P14 potential in coma and brain death. Brain 1996;119:1507–1521.

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Eelco F.M. Wijdicks, Panayiotis N. Varelas, Gary S. Gronseth and David M. Greer

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