Winkfield v. Childrens Hospital Oakland et al Doc. 15 Att. 4

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CHILDREN'S HOSPITAL & RESEARCH
CENTER AT OAKLAND

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

LATASHA WINKFIELD, as an Individual, and as Guardian Ad Litem and mother of Jahi McMath,

Plaintiff,

v.

CHILDREN'S HOSPITAL & RESEARCH CENTER AT OAKLAND; DR. DAVID DURAND, and Does 1-100, inclusive,

Defendants.

Case No. 4:13-cv-05993-SBA

DECLARATION OF DR. HEIDI FLORI OPPOSING PETITIONER'S REQUEST FOR COURT ORDER COMPELLING CHILDERN'S HOSPITAL TO PERFORM TRACHEOSTOMY AND INSERT GASTROINTESTINAL TUBE

Date: 1/17/14
Time: 1:00 P.M.
Location: Dept. 1, 4th Flr
1301 Clay St., Oakland
Judge: Hon. Saundra Brown Armstrong

Dockets.Justia.com

I, Heidi Flori, M.D., hereby declare as follows:

1. I am a physician licensed in the State of California. I am board certified in pediatrics as well as pediatric critical care medicine. I have been on the medical staff at Children's Hospital & Research Center Oakland ("Children's") since 1998 and Medical Director of the Pediatric Intensive Care unit at Children's since 2009.

2. I have intermittently taken care of Jahi McMath's body since her death on December 11-12, 2013. In addition, I have discussed the case and management in detail with my colleagues in the Pediatric Intensive Care Unit who have been caring for Ms. McMath's body during that time in order to be completely apprised of events and the course of action being required of us by the courts.

3. It has been noted by the members of the medical team that Ms. McMath has intermittently had movements of her arms, shoulders, legs and toes. These are the same types of movements shown on the video(s) that have been submitted by Mrs. Winkfield for court review in the pending legal proceedings, which videos I have reviewed. These movements have all been consistent with "brain death-associated reflexes" and "automatisms" (automatic behavior) and do not signal that Ms. McMath is alive. *See,* S. Jain and M. DeGeorgia, *Brain Death-Associated Reflexes and Automatisms,* Neurocritical Care 2005, 3:122-126, a true and correct copy of this article is attached to this declaration as Exhibit A.

4. In their review, Jain and DeGeorgia found that movements in brain dead bodies are frequently reported in the literature (15-60% of cases) and the reported movement included undulating (wave like) toe movements, unusual facial movements, abnormal body posturing, respiratory-like movements, hugging-like motion, eyelid opening, head turning, limb elevation with neck flexion and other spinal reflexes (*Brain Death-Associated Reflexes and Automatisms, supra*, 3:122-126.) It is understood that these reflexes generate from the spinal cord and are particularly prominent because of the lack of any modulation from the dead brain.

5. In 1995, the American Academy of Neurology established criteria for the diagnosis of brain death and also described movements that may be present despite brain death including "[s]pontaneous movements of limbs other than pathologic flexion or extension response"; "[r]espiratory-like movements (shoulder elevation and adduction, back arching, intercostal expansion without significant tidal volumes)"; and "[d]eep tendon reflexes; superficial abdominal reflexes; [and] triple flexion response . . . ." . (*See, Practice Parameters for Determining Brain Death in Adults (Summary Statement)*, Neurology 1995;45:1012-1014, a true and correct copy of this article is attached to this declaration as Exhibit B.).

6. In 2010, the American Academy of Neurology indicated that such movements may include, but are not limited to "facial myokymia [fine facial movements], transient bilateral finger tremor, repetitive leg movements, ocular microtremor [eye tremors], and cyclical constriction and dilatation in light-fixed

pupils [abnormal exaggeration of the rhythmic contraction and dilation of the pupil, independent of changes in illumination or in fixation of the eyes]." (*See, Evidence-based guideline update: Determining Brain Death in Adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology,* American Academy Neurology 2010;74:1911, 1912; a true and correct copy of this article is attached to this declaration as Exhibit C.)

7. The medical team has seen no indications of Ms. McMath's body spontaneously initiating breaths. However, the medical team has reported that ventilator "autocycling" did occur at least on one occasion and the ventilator circuit and filter did need to be exchanged. This type of technical ventilator issue is common in the pediatric intensive care unit. A lay observer could mistakenly believe this showed the patient attempting to take a breath when in actuality, it is merely a reflection of excessive humidity or deposit accumulation in ventilator tubing or ventilator filters that then simply need to be exchanged. The American Academy of Neurology has also commented on this ventilator phenomenon potentially falsely impacting the evaluation of respiration in their 2010 update. See *Determining Brain Death in Adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology, supra*, at p. 1912; see also *Practice Parameters for Determining Brain Death in Adults, supra,* at p. 1013. Such ventilator activity is absolutely not an indication that Ms. McMath is alive. Her body has completely failed multiple apnea tests designed to test the body's ability to breathe without the ventilator.

8. It is important to note that the literature on movement after brain death does not extend to observations beyond 72 hours, because brain dead individuals are traditionally not left on a ventilator longer than this. Given the unprecedented actions taken to date in this case, we anticipate that muscle activity, particularly the potential for increased muscle tone, may continue over time as well as spinal reflexes given that Ms. McMath's body is being sustained by the following: the mechanical ventilator; meticulous corporal care by the nursing and respiratory teams; and continued sources of hydration, salts and simple carbohydrates in her intravenous fluids. Despite this, the body continues to deteriorate with gradual decrease in her blood pressure over time. Ms. McMath is no longer alive.

I declare under the penalty of perjury under the laws of the State of California and the United States that the foregoing is true and correct. Executed this 2nd day of January, 2014 at Oakland, California.

Heidi R. Flori, MD

EXHIBIT A

Exhibit A

S. Jain and M. DeGeorgia
Brain Death-Associated Reflexes and Automatisms
(Attached)

Exhibit-A

Neurocritical Care
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Original Article

Brain Death-Associated Reflexes and Automatisms

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Abstract

Background: In several instances, the diagnosis of brain death has been questioned due to the presence of movements. This case report and review of the literature illustrates the spectrum of movements that have been encountered in brain death.

Methods: A case report and review of the literature on movements seen in brain death was conducted.

Results: Movements in brain death are common and have a wide range of phenomenology. Several movements wax and wane over time, making movements in brain death difficult to classify. In addition, varying terminology has been used (e.g., Lazarus sign, spinal man, spinal reflexes, spinal automatisms). Although evidence points to a spinal origin for such movements, the pathophysiology in many cases remains speculative. Characteristics of movements in brain death have been identified that can help differentiate them from brainstem or voluntary origin.

Conclusions: Based on our review, we suggest referring to stimulus-provoked movements as reflexes and spontaneous movements as automatisms. We propose using the terms *brain death-associated reflexes* and *brain death-associated automatisms* as two main categories for movements that occur in brain death. These terms do not imply a specific pathophysiology, but consistent clinically oriented nomenclature may be useful when reporting such phenomena.

(Neurocrit. Care 2005;3:122–126)

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Humana Press

Background

Brain death is defined as the permanent absence of cortical and brainstem function. The growth of critical care has contributed to the need for accurate and timely diagnosis of brain death. Occasionally, certain movements may raise the possibility of persistent brainstem function, such as the spinal cord-generated endotracheal suction-thoracic contraction reflex that can mimic a cough reflex. We present an illustrative case report and review the literature on the spectrum of movements observed in the setting of brain death. To improve clarity in reporting, we also suggest a consistent nomenclature for these movements.

Methods

A retrospective review of handwritten and electronic records of a patient with motor activity in the presence of brain death was conducted, followed by a review of the literature. The Institutional Review Board of The Cleveland Clinic Foundation approved this study.

Case Report

A 41-year-old man presented with dyspnea and hypoxia after 1 week of cough, pleuritic chest pain, nausea, and vomiting. Pulmonary embolism was suspected, and he was anticoagulated with intravenous heparin. Shortly thereafter, he developed asystole and ventricular fibrillation. He was resuscitated after 15 minutes but again developed asystole. Echocardiography demonstrated a large pericardial effusion, and a pericardiocentesis was immediately performed. Return of spontaneous circulation occurred after 23 minutes.

Neurological examination found him to be intubated and comatose. He had spontaneous and frequent eye opening that was not stimulus sensitive. Pupils were minimally reactive bilaterally. Eyes were straight ahead with no movement with oculo-cephalic maneuvers. Corneal and gag reflexes were absent, although he was breathing spontaneously above the set ventilator rate. There were no limb movements to painful stimulation. He had myoclonic jerks of the face and body, with bilateral lower extremity adductor myoclonic movements. Muscle stretch reflexes were present in the upper extremities and absent in the lower extremities. Babinski sign was absent. A brain computed tomography scan showed effacement of the basal cisterns consistent with early brain edema.

Later that day, the patient again developed ventricular fibrillation terminated by countershock. Echocardiography showed a small residual pericardial hematoma. The next day, the patient had fixed and dilated pupils and bilateral papilledema. He had no spontaneous respirations and no brainstem reflexes, fulfilling brain death criteria. Motor examination demonstrated triple flexion of the lower extremities. In the upper extremities, noxious stimulation of the right arm resulted in ipsilateral flexion at the elbow and supination of the arm, bringing the forearm to rest on the patient's abdomen. Minute flexion and extension movements occurred spontaneously in the toes. These movements persisted for 5 days after the anoxic event. Electroencephalography revealed electrocerebral silence.

Review of the Literature

History

Movements occurring in the setting of death have been noted for centuries. During the French Revolution, body movements among the beheaded, such as eyelid and jaw contraction, were frequently observed. The guillotine usually cut through the lower part of the fourth cervical vertebra *(1)*. Brain death was formally defined in 1968 as the irreversible loss of cerebral and brainstem function *(2)*. At that time, the presence of any spontaneous or reflex movements invalidated the diagnosis. Since then, several other criteria have been published that account for brain death-associated motor activity *(3)*.

Most of the literature on this subject includes case reports or small series. A summary of the literature is provided in Table 1. Major difficulty in discussing such movements is the lack of consistent terminology or categorization. Discussion could be organized in terms of phenomenology, time of appearance after brain death, pathophysiology, or phylogentically. We chose to organize our review by phenomenology, because this category is the least speculative and would likely be of most clinical use. We then briefly discuss time of onset and pathophysiology.

When describing movements in the presence of breath death, there can be linguistic challenges *(1)*. Once a patient is declared brain dead, some have argued it is inappropriate to continue to use the term "patient." In the literature, terms include "heart-beating cadavers" *(1)*, "spinal man" *(4)*, and "brain dead body" *(5)*. In this review, we prefer the simple term of brain dead body.

Epidemiology

Ivan retrospectively reviewed 52 brain dead bodies and found muscle stretch reflexes in 35%, plantar flexor responses in 60%, plantar withdrawal in 35%, and abdominal reflexes in 75% *(6)*. In the same year, Jorgensen introduced the term "spinal man" in reference to such phenomena *(4)*. In his series of 63 brain dead bodies, he found a withdrawal response in the lower limbs in 79%, and muscle stretch reflexes in 49% of upper extremities and 33% of lower extremities. Jorgensen first described extension and pronation of the arm in response to cutaneous stimulation, seen in one-third of brain dead bodies.

Saposnik and coworkers prospectively evaluated spontaneous and reflex movements in 38 brain dead bodies *(7)* through noxious stimuli to the sternum, four limbs, and supraorbital area; neck flexion; tactile stimulation to the palms of hands and soles of feet; and elevation of four limbs. Thirty-nine percent of brain dead bodies had either spontaneous or reflex movements. These movements were observed mainly within the first 24 hours after declaration of brain death and consisted of spontaneous jerks of the fingers, undulating toe flexion, triple flexion, unilateral facial myokymia, "Lazarus sign," upper limb pronation/extension reflex, and flexor plantar response. In another study, Dösemeci and coworkers found similar spinal reflexes in 18 of 134 brain dead bodies (13.4%) *(7)*. Saposnik and coworkers reported movements in 47 out of 107 brain dead bodies (44%) *(8)*.

Conci and coworkers looked at 25 brain dead bodies during kidney removal with a mean time on the ventilator before nephrectomy of 31 ± 6 hours *(9)*. Abdominal muscle contraction was noted in 60% of brain dead bodies when the parietal peritoneum was cut. Twenty-four percent had sudden changes in blood pressure and heart rate during the incision. No response was seen to bowel manipulation.

Patterns of Motor Activity

Movements that have been studied in brain dead bodies are numerous. What follows is not intended to be a comprehensive listing of all movements documented in brain death. Rather, patterns of well-documented motor activity in the presence of brain death are summarized. This summary includes polysegmental spinal reflexes and automatisms, "Lazarus sign," undulating toe sign (undulating toe flexion movements), eyelid opening, respiratory-like movements, head turning, pseudodecerebrate posturing, facial myokymin, eyelid opening, abdominal movements, upper and lower facial movements, eyelid and tongue myoclonus, and spinal myoclonus.

Spittler and coworkers focused on systematically describing polysegmental spinal reflex patterns and polysegmental spinal automatism patterns in brain death *(5)*. They categorized spinal movements as monosegmental muscle stretch reflexes, oligosemental cutaneo-muscular reflexes, polysegmental spinal reflex patterns (PSRPs), polysegmental spinal automatism patterns (PSAPs), and "Lazarus sign."

Spittler et al. examined 235 patients on 278 examinations for brain death. Interindividual and intraindividual phenomenological variability was noted. Thus, the authors set out to distinguish characteristics by which PSRPs and PSAPs can be differentiated from voluntary or brainstem-generated involuntary movements. They assigned the loss of pupillary light reflex as the start of the brain death process and loss of the cough reflex the completion of the brain death process.

Spinal movements were observed on 42 occasions in 27 of the brain dead bodies. Up to five distinct spinal reflexes were observed in a single body. Thirty-one different spinal reflexes

Table 1
Brain Death-Associated Movements

Movement	*Description*	*Onset after BD dx*	*Age, sex (M/F)*	*Source (no. of subjects)*	*Automatism or reflex*[a]
Lazarus sign[b]	Seems to be grasping for endotracheal tube: one or both arms flexed at elbows with hands brought to chin or face and then returned to the bed beside the body; reported spontaneously, during apnea testing, and with neck flexion during transcranial doppler examination	0–2 days	26/67 M/F	Heytens et al. (1)[14] Ropper (5)[15] de Freitas et al. (4)[10] Urasaki et al. (1)[11] Turmel et al. (2)[12] Jastremski et al. (1)[13]	Automatism and reflex
Undulating toe	Slow flexion/extension movements of toes, spontaneous or elicited by tactile/noxious plantar stimulation	NA	NA	McNair et al. (3)[24] Saposnik et al. (25)[8]	Automatism and reflex
Unusual facial movements	Flaring of alae nasi	NA	14 M	Rodrigues et al. (1)[26]	Automatism
Extensor posturing	Asymmetrical opisthotonus (back arching to left or right spontaneously)	2 days	51 M	Heytens et al. (1)[14]	Automatism
Facial myokymia	Intermittent repetitive undulating muscle contractions of left cheek	NA	54M	Saposnik et al. (1)[8]	Automatism
Spinal myoclonus	Multifocal myoclonus involving lower limbs and abdominal muscles lasting 15 hours, bilateral and asymmetric, causing the body to jump over the bed	6 days	56 M	Fujimoto et al. (1)[29]	Automatism
Respiratory-like movements	Both shoulders adduct and slow cough-like movements minutes after respirator removal	35 minutes	67 F	Urasaki et al. (1)[11] Ropper (5)[15]	Automatism
Hugging-like motion	Sudden hugging-like motion with both arms and flexion of the trunk to 30° for a few seconds	NA	NA	Aranibar (1)[20]	Automatism
Decerbrate-type movements	Spontaneous decerebrate type movements in all four extremities	24 hours	35 M	Jastremski et al. (1)[13]	Automatism
Eyelid opening	Left or bilateral eyelid opening with noxious stim to ipsilateral nipple	24 hours	57 M	Friedman (1)[27]	Reflex
Head turning	Inconsistent extension of both upper extremities at the elbow and wrist after noxious stimulation; head intermittently turns from side to side for 10–30 seconds with passive neck flexion, extension, or sternal rub	4 days	42 M	Christie et al. (1)[22]	Reflex
Decerebrate-like posturing with mechanical ventilation	Symmetric movements lasting 5 seconds in both arms with hyperpronation and forearm extension, wrist flexion, metacarpophalangeal joint extension, and interphalangeal joint flexion synchronously triggered by insufflation of mechanical ventilation and by superficial pressure or noxious stimulation to the arms, thorax, or abdomen	Immediate	30 F, 11-month-old boy	Marti-Fabregas et al. (2)[23]	Reflex
Limb elevation with neck flexion	A rapid jerk raising all four limbs off the bed 0.5–8 inches with passive neck flexion	NA	NA	Ropper (5)[15]	Reflex
Viscero-somatic reflex	Contraction of the abdominal musculature after parietal peritoneum was cut during organ harvest	Immediate	15–61, M and F	Conci et al. (15)[9]	Reflex
Other studies					
Spinal reflexes and automatisms	31 different reflexes and 4 automatisms in 11% of 235 BD bodies	NA	NA	Spittler et al. (27)[5]	4 automatisms and 31 reflexes
Spinal reflexes	7 different reflexes in 79% of 63 BD bodies	0–72 hours	NA	Jorgensen (50)[4]	Reflex
Spinal reflexes	7 different reflexes in almost 75% of 52 bodies	0 hours	NA	Ivan (~39)[6]	Reflex
Spinal reflexes	6 different reflexes in 13% of 134 bodies	0–72 hours	NA	Dosemeci (18)[7]	Reflex

NA, not available.

[a]Reflexes are defined as movements elicited by a defined stimulus, and automatisms are spontaneous movements.

[b]The term Lazarus sign was not used in all published material. We listed studies in this category if the cases matched the phenomenology described. Features associated with the Lazarus sign include occuring with apnea test (2–8 minutes after vent disconnected), hypertension, hypotension, tachycardia, facial flushing, gooseflesh on arms and trunk, and shivering extensor movements.

Source reference numbers indicated in superscript.

and four different spinal automatisms were documented. When discussing their findings, Spittler et al. stated, "The variable elicitation mechanisms and the different patterns of reflexes and automatisms make a systematical classification difficult: A uniform registration even of latency and duration for all forms of reflexes is not feasible and in cases of automatisms is impossible" (5). Dösemeci and coworkers described spinal reflexes which included the Lazarus sign, flexion of the arms with abduction of the shoulders, extension at the arms and shoulders, and flexion of the arms and feet. The most common movement they reported was finger and toe jerk (7). Saposnik and coworkers found undulating toe flexion movements to be the most common, seen in 23% of brain dead bodies (8).

Spittler et al. noted wide interindividual variation, and most patterns were observed in only one body. However, salient characteristics of polysynaptic spinal reflexes and automatisms were found, which can be useful when attempting to rule out brainstem activity. Spinal movements were found to have stereotypical elicitation upon a trigger of limited variation, constant pattern of latency and duration, habituation with frequent triggers (refractory period), no habituation with slow sequence of triggers, similarity of reflexes and automatisms, and a monotone stereotyped course of the motor pattern. Well-documented brain death movement patterns are summarized in Table 1.

Timing of Movements in the Course of Brain Death

Although most movements are observed within the first 24 hours after the declaration of brain death, the timing can be highly variable (hours to days). The timing of brain death is defined by the time a clinical brain death exam fits accepted criteria, which may be seconds, minutes, hours, or days after physiological brain function has ceased. Jorgensen made the observation that those who lost spinal reflexes and regained them did so within 6 hours (4). This timing occurred with the flexion-withdrawal response first, followed by the cremasteric and abdominal reflexes, and then muscle stretch reflexes. The delayed appearance of spinal reflexes was invariably associated with severe arterial hypotension. Dösemeci noted that all spinal reflexes were seen during the first 24 hours after brain death was confirmed and remitted by 72 hours (7). Undulating toe flexion movements are more likely to be seen in the first 12 hours after the diagnosis of brain death (8).

Pathophysiology

The spinal cord is the putative source for movement of the brain dead body. Various mechanisms have been proposed for these movements. Conci and coworkers proposed that spinal reflexes are present in brain death if the ischemic lesion is above C1–C4 (9). Within the spinal cord, neuronal networks exist that serve as central generators for specific motor patterns (1). Corticospinal and rubrospinal tracts located in the lateral funiculus control distal portions of the limbs. Vestibulospinal and reticulospinal tracts modulate tone and posture, contributing to synergistic movement of an entire limb. Supraspinal disconnection of these tracts may increase their excitability at the spinal level, resulting in spinal movements emerging during brain death. However, this possibility has not been thoroughly studied, and the precise physiology is unknown.

Spittler and coworkers proposed that some spinal reflexes can be considered phylogenetically "old motor patterns," which may be set free when the cord is uncoupled from the "younger" input of the brainstem and neocortex. This perspective allows an orderly categorization of some observed phenomena. In this schema, spinal reflexes or automatisms that do not have an apparent evolutionary purpose can be understood as disintegration or irradiation of spinal circuitry. The temporal variability of the emergence of spinal reflexes has been explained by spinal shock that can be observed after brain death (6).

Lazarus sign has been reported to occur spontaneously, after respirator removal, during apnea testing, in the setting of arterial hypotension, noxious stimuli, or passive neck flexion (7,9–14). It has been thought to result from hypoxic stimulation of cervical spinal cord neurons functionally isolated from rostral brain areas. Supportive of this concept was the finding by de Freitas and coworkers of complex spinal reflexes in a subset of brain dead bodies with lower systolic blood pressures (10). Mechanical stimulation of spinal roots, cord, or sensory neurons also may contribute to this complex movement (15).

Hanna and Frank comment that automatic stepping is a spinal automatism that occurs in animals after transaction at the superior colliculus level and cite evidence that supports a spinal pattern generator for locomotion (16). Stepping motions occur in patients before brain death when brain inhibition is released and transmission is continued in the ventral spinal cord and brainstem motor tracts.

Short-latency somatosensory evoked potentials have been recorded in the presence of upper and lower extremity movements during brain death (8,11). During arm movements no responses were recorded on scalp electrodes except far-field components. The spinal N13 component was preserved. Auditory brainstem-evoked potentials were absent for both ears, demonstrating preserved spinal dorsal horn potentials in the presence of movements. Further evidence for such movements being spinal in origin comes from Saposnik and coworkers. In five brain dead bodies that had undulating toe flexion movements, SSEPs did not elicit cortical responses (8). Urasaki and coworkers postulated that respiratory-like movements can be spinal in origin (11).

Facial myokymia is a movement that has been studied by the orbicularis oculi reflex and facial nerve stimulation. When tested, the early and late components of the orbicularis oculi reflex were found to absent bilaterally, whereas peripheral nerve conduction was preserved. This finding suggests facial myokymia in brain death is due to muscle denervation (2).

Discussion

Our review shows that movements in brain dead bodies are common and display a wide spectrum of phenomenology. The terms "automatism" and "reflex" have been used inconsistently, at times referring to the same movement. We suggest referring to stimulus-provoked movements as reflexes and spontaneous movements as automatisms. In the setting of brain death, we propose using the terms *brain death-associated reflexes* and *brain death-associated automatisms*. This terminology is clinically useful because all movements reported in brain dead bodies can be placed in one of these two categories.

Furthermore, it does not imply a particular mechanism, which remains speculative in some cases. Although primarily descriptive, these terms have important implications. Brain death-associated reflexes are stimulus provoked movements that do not contradict the diagnosis of death. Such movements may or may not be present during life. Thus, subsets of these reflexes include muscle stretch reflexes, abdominal reflexes, and plantar flexion. Likewise, brain death-associated automatisms are spontaneous movements that do not contradict the diagnosis of death.

Brain death-associated reflexes and automatisms can be time dependent, emerging or resolving depending on the time elapsed from the onset of brain death. If possible, it is important to determine the time elapsed from declaration of brain death to the onset of movements. Most reported brain stem-associated reflexes are no longer present 72 hours after brain death declaration. Certain characteristics are typical of movements in brain death that can help differentiate them from voluntary or brainstem-derived motor activity *(5)*. Evoked potentials may be helpful when the spinal origin of a particular movement is questioned *(11)*.

The diagnosis of breath death has evolved to incorporate the observations of brain death associated reflexes and automatisms. In 1995, the American Academy of Neurology established criteria for the diagnosis of brain death which included certain movements as acceptable findings *(16)*. These manifestations are occasionally seen and should not be misinterpreted as evidence for brainstem function:

1. Spontaneous movements of limbs other than pathological flexion or extension response.
2. Respiratory-like movements (shoulder elevation and adduction, back arching, intercostal expansion without significant tidal volumes).
3. Sweating, blushing, tachycardia.
4. Normal blood pressure without pharmacological support or sudden increases in blood pressure.
5. Absence of diabetes insipidus.
6. Deep tendon reflexes, superficial abdominal reflexes, triple flexion response.
7. Babinski reflex.

However, movements in the setting of brain death still cast doubt on the diagnosis *(7)*, resulting in consideration of confirmatory testing and prolonged treatment. When clinical criteria for brain death are met, the recognition of brain death-associated movements can reduce uncertainty of death and reliance on confirmatory testing. Greater awareness of such motor activity can reduce doubt for clinicians and provide an explanation for families in the difficult situation of witnessing brain death-associated movements.

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EXHIBIT B

Exhibit B

Practice Parameters for Determining Brain Death in Adults (Summary Statement)
(Attached)

Exhibit B

special article

NEUROLOGY 1995;45:1012-1014

Practice parameters for determining brain death in adults
(Summary statement)

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

Overview. Brain death is defined as the irreversible loss of function of the brain, including the brainstem. Brain death from primary neurologic disease usually is caused by severe head injury or aneurysmal subarachnoid hemorrhage. In medical and surgical intensive care units, however, hypoxic-ischemic brain insults and fulminant hepatic failure may result in irreversible loss of brain function. In large referral hospitals, neurologists make the diagnosis of brain death 25 to 30 times a year.

Justification. Brain death was selected as a topic for practice parameters because of the need for standardization of the neurologic examination criteria for the diagnosis of brain death. Currently, there are differences in clinical practice in performing the apnea test and controversies over appropriate confirmatory laboratory tests. This document outlines the clinical criteria for brain death and the procedures of testing in patients older than 18 years.

Description of the process. All literature pertaining to brain death identified by MEDLINE for the years 1976 to 1994 was reviewed. The key words "brain death" and "apnea test" (subheading, "adult") were used. Peer-reviewed articles with original work were selected. Current textbooks of neurology, medicine, pulmonology, intensive care, and anesthesia were reviewed for opinion. On the basis of this review and expert opinion, recommendations are presented as standards, guidelines, or options. *The recommendations in this document are guidelines unless otherwise specified (see boxed Definitions at end).*

I. Diagnostic criteria for clinical diagnosis of brain death

A. Prerequisites. Brain death is the absence of clinical brain function when the proximate cause is known and demonstrably irreversible.
1. Clinical or neuroimaging evidence of an acute CNS catastrophe that is compatible with the clinical diagnosis of brain death
2. Exclusion of complicating medical conditions that may confound clinical assessment (no severe electrolyte, acid-base, or endocrine disturbance)
3. No drug intoxication or poisoning
4. Core temperature ≥32 °C (90 °F)

B. The three cardinal findings in brain death are coma or unresponsiveness, absence of brainstem reflexes, and apnea.
1. Coma or unresponsiveness—no cerebral motor response to pain in all extremities (nail-bed pressure and supraorbital pressure)
2. Absence of brainstem reflexes
   a. Pupils
      (i) No response to bright light
      (ii) Size: midposition (4 mm) to dilated (9 mm)
   b. Ocular movement
      (i) No oculocephalic reflex (testing only when no fracture or instability of the cervical spine is apparent)
      (ii) No deviation of the eyes to irrigation in each ear with 50 ml of cold water (allow 1 minute after injection and at least 5 minutes between testing on each side)
   c. Facial sensation and facial motor response
      (i) No corneal reflex to touch with a throat swab
      (ii) No jaw reflex
      (iii) No grimacing to deep pressure on nail bed, supraorbital ridge, or temporomandibular joint
   d. Pharyngeal and tracheal reflexes
      (i) No response after stimulation of the posterior pharynx with tongue blade
      (ii) No cough response to bronchial suctioning

See also page 1003

Approved by the Quality Standards Subcommittee July 20, 1994. Approved by the Practice Committee July 29, 1994. Approved by the Executive Board September 24, 1994.

Address correspondence and reprint requests to Joanne F. Okagaki, American Academy of Neurology, Suite 335, 2221 University Ave., SE, Minneapolis, MN 55414. The background paper by Dr. Eelco F.M. Wijdicks, published in this issue, is also available upon request from the American Academy of Neurology office (612/623-2439).

3. Apnea—testing performed as follows:
   a. Prerequisites
      (i) Core temperature ≥36.5 °C or 97 °F
      (ii) Systolic blood pressure ≥90 mm Hg
      (iii) Euvolemia. *Option:* positive fluid balance in the previous 6 hours
      (iv) Normal P_{CO_2}. *Option:* arterial P_{CO_2} ≥40 mm Hg
      (v) Normal P_{O_2}. *Option:* preoxygenation to obtain arterial P_{O_2} ≥200 mm Hg
   b. Connect a pulse oximeter and disconnect the ventilator.
   c. Deliver 100% O_2, 6 l/min, into the trachea. *Option:* place a cannula at the level of the carina.
   d. Look closely for respiratory movements (abdominal or chest excursions that produce adequate tidal volumes).
   e. Measure arterial P_{O_2}, P_{CO_2}, and pH after approximately 8 minutes and reconnect the ventilator.
   f. If respiratory movements are absent and arterial P_{CO_2} is ≥60 mm Hg (*option:* 20 mm Hg increase in P_{CO_2} over a baseline normal P_{CO_2}), the apnea test result is positive (ie, it supports the diagnosis of brain death).
   g. If respiratory movements are observed, the apnea test result is negative (ie, it does not support the clinical diagnosis of brain death), and the test should be repeated.
   h. Connect the ventilator if, during testing, the systolic blood pressure becomes ≤90 mm Hg or the pulse oximeter indicates significant oxygen desaturation and cardiac arrhythmias are present; immediately draw an arterial blood sample and analyze arterial blood gas. If P_{CO_2} is ≥60 mm Hg or P_{CO_2} increase is ≥20 mm Hg over baseline normal P_{CO_2}, the apnea test result is positive (it supports the clinical diagnosis of brain death); if P_{CO_2} is <60 mm Hg or P_{CO_2} increase is <20 mm Hg over baseline normal P_{CO_2}, the result is indeterminate, and an additional confirmatory test can be considered.

II. Pitfalls in the diagnosis of brain death

The following conditions may interfere with the clinical diagnosis of brain death, so that the diagnosis cannot be made with certainty on clinical grounds alone. Confirmatory tests are recommended.

A. Severe facial trauma
B. Preexisting pupillary abnormalities
C. Toxic levels of any sedative drugs, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptic drugs, chemotherapeutic agents, or neuromuscular blocking agents
D. Sleep apnea or severe pulmonary disease resulting in chronic retention of CO_2

III. Clinical observations compatible with the diagnosis of brain death

These manifestations are occasionally seen and should not be misinterpreted as evidence for brainstem function.

A. Spontaneous movements of limbs other than pathologic flexion or extension response
B. Respiratory-like movements (shoulder elevation and adduction, back arching, intercostal expansion without significant tidal volumes)
C. Sweating, blushing, tachycardia
D. Normal blood pressure without pharmacologic support or sudden increases in blood pressure
E. Absence of diabetes insipidus
F. Deep tendon reflexes; superficial abdominal reflexes; triple flexion response
G. Babinski reflex

IV. Confirmatory laboratory tests (*Options*)

Brain death is a clinical diagnosis. A repeat clinical evaluation 6 hours later is recommended, but this interval is arbitrary. A confirmatory test is not mandatory but is desirable in patients in whom specific components of clinical testing cannot be reliably performed or evaluated. It should be emphasized that any of the suggested confirmatory tests may produce similar results in patients with catastrophic brain damage who do not (yet) fulfill the clinical criteria of brain death. The following confirmatory test findings are listed in the order of the most sensitive test first. Consensus criteria are identified by individual tests.

A. Conventional angiography. No intracerebral filling at the level of the carotid bifurcation or circle of Willis. The external carotid circulation is patent, and filling of the superior longitudinal sinus may be delayed.
B. Electroencephalography. No electrical activity during at least 30 minutes of recording that adheres to the minimal technical criteria for EEG recording in suspected brain death as adopted by the American Electroencephalographic Society, including 16-channel EEG instruments.
C. Transcranial Doppler ultrasonography
   1. Ten percent of patients may not have temporal insonation windows. Therefore, the initial absence of Doppler signals cannot be interpreted as consistent with brain death.
   2. Small systolic peaks in early systole without diastolic flow or reverberating flow, indicating very high vascular resistance associated with greatly increased intracranial pressure.
D. Technetium-99m hexamethylpropyleneamineoxime brain scan. No uptake of isotope in brain parenchyma ("hollow skull phenomenon").

E. Somatosensory evoked potentials. Bilateral absence of N20-P22 response with median nerve stimulation. The recordings should adhere to the minimal technical criteria for somatosensory evoked potential recording in suspected brain death as adopted by the American Electroencephalographic Society.

V. Medical record documentation (*Standard*)

A. Etiology and irreversibility of condition
B. Absence of brainstem reflexes
C. Absence of motor response to pain
D. Absence of respiration with $P_{CO_2} \geq 60$ mm Hg
E. Justification for confirmatory test and result of confirmatory test
F. Repeat neurologic examination. *Option:* the interval is arbitrary, but a 6-hour period is reasonable.

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The Quality Standards Subcommittee wishes to express particular gratitude to Eelco F.M. Wijdicks, MD, for his work in preparing the background paper as well as this summary statement. Jasper R. Daube, MD, served as facilitator for this project. The Quality Standards Subcommittee thanks the Ethics and Humanities Subcommittee and the fifteen members of the AAN Member Reviewer Network who reviewed and returned comments on these practice parameters. The Subcommittee appreciates the reviews of several other critical care specialists.

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Medical societies invited to comment on these practice parameters: the American Academy of Family Physicians (which provided comment), the American Association of Neurological Surgeons, and the American Academy of Pediatrics.

DEFINITIONS

Classification of evidence

Class I. Evidence provided by one or more well-designed, randomized, controlled clinical trials.

Class II. Evidence provided by one or more well-designed clinical studies such as case-control and cohort studies.

Class III. Evidence provided by expert opinion, nonrandomized historical controls, or one or more case reports.

Strength of recommendations

Standards. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on class I evidence or, when circumstances preclude randomized clinical trials, overwhelming evidence from class II studies that directly addresses the question at hand or from decision analysis that directly addresses all the issues).

Guidelines. Recommendations for patient management that may identify a particular strategy or range of management strategies and that reflect moderate clinical certainty (ie, based on class II evidence that directly addresses the issue, decision analysis that directly addresses the issue, or strong consensus of class III evidence).

Practice options or advisories. Strategies for patient management for which clinical certainty is lacking (ie, based on inconclusive or conflicting evidence or opinion).

Practice parameters. Results, in the form of one or more specific recommendations, from a scientifically based analysis of a specific clinical problem.

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 methods. The AAN recognizes that specific decisions on patient care are the prerogative of the patient and the physician caring for the patient and are based on all the circumstances involved. Regardless of the conclusions of this statement, the Quality Standards Subcommittee of the AAN recognizes the need to comply with state law.

EXHIBIT C

Exhibit C

Evidence-based guideline update: Determining Brain Death in Adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology

(Attached)

Exhibit C

SPECIAL ARTICLE

Evidence-based guideline update: Determining brain death in adults

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

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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 99mHexamethazime; 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-

Supplemental data at www.neurology.org

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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.[4]

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-

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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]

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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

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$PaCO_2$, 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.

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- 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 Abbott 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

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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 credible 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 hexamethazime(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 ≥ 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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