Neuroanesthesia and Intensive Care

Brief review: History, concept and controversies in the neurological determination of death

[Revue sommaire : histoire, concept et discussion de la détermination neurologique de la mort]

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Purpose: Despite general worldwide acceptance of the concept of neurological determination of death (NDD), inconsistencies in clinical criteria and ancillary testing requirements remain. Numerous guidelines for NDD may be applied in clinical practice by a variety of medical practitioners, but the scientific rationale for specific guideline recommendations often remains unclear. This review examines the evolution of NDD, and seeks to provide scientific validation for existing NDD criteria.

Source: English language peer-reviewed medical journals and established contemporary medical texts.

Principal findings: Currently published guidelines appear to have evolved from the work of the ad hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. The Conference of the Royal Colleges and Faculties of the United Kingdom refined the criteria and subsequently adopted the principal of brainstem death. While the fundamentals of NDD guidelines are remarkably consistent worldwide, specific criteria and requirements are often inconsistent.

Conclusion: Numerous controversies regarding NDD continue to exist, necessitating further scientific clarification of these issues. More recently published guidelines representing the collective opinion of world experts in NDD based upon best current scientific evidence are available in current medical journals.

***Objectif** : Malgré l'acceptation mondiale du concept de détermination neurologique de la mort (DNM), un manque d'homogénéité persiste dans les critères cliniques et les exigences de tests accessoires. De nombreuses directives peuvent être appliquées pour la DNM par divers praticiens médicaux cliniques, mais le fondement scientifique des recommandations de pratique demeure souvent confus. La présente revue examine l'évolution de la DNM et cherche à donner une validation scientifique aux critères existants de DNM.*

***Source** : Des revues médicales de langue anglaise vérifiées par des pairs et des textes médicaux contemporains reconnus.*

***Constatations principales** : Les directives publiées présentement paraissent avoir évolué depuis le premier travail du Comité spécial de la Harvard Medical School chargé de définir la mort encéphalique. La Conference of the Royal Colleges and Faculties of the United Kingdom a raffiné les critères et subséquemment adopté le principe de mort du tronc cérébral. Quoique le fondement des directives sur la DNM soit remarquablement cohérent à travers le monde, les exigences et les critères spécifiques sont souvent irréguliers.*

***Conclusion** : Beaucoup de controverse continue d'exister en regard de la DNM, ce qui nécessite une clarification scientifique poussée. Des directives publiées plus récemment sont accessibles. Elles font part de l'opinion collective d'experts mondiaux en DNM, fondée sur la meilleure preuve scientifique actuelle.*

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IN its 1999 practice guideline, the Canadian Neurocritical Care Group defined brain death as "the irreversible loss of the capacity for consciousness combined with the irreversible loss of all brainstem functions including the capacity to breathe".[1] This definition of death is generally widely accepted by the mainstream medical community and the lay public to be equivalent to a traditional circulatory formulation of death defined by the cessation of tissue perfusion, and detected by the absence of peripheral pulses and spontaneous respiration.

Brain-based determination of death has also received statutory recognition in many jurisdictions worldwide. In the United States, neurological criteria for brain death were acknowledged in the Uniform Determination of Death Act (UDDA). [2] It is noteworthy that the UDDA does not embody a standard by which brain death is determined. Rather, it acknowledges that brain death should be determined "in accordance with accepted medical standards". Although this act provides latitude to accommodate a better understanding of the pathophysiology of brain death and evolution of diagnostic medical technologies, it has undoubtedly contributed to a burgeoning number of guidelines for brain death determination.

Guidelines prepared by those with a special interest in brain death determination have existed in Canada since 1987.[3] In spite of this, individual hospitals and health care regions have adopted local guidelines which vary from more widely accepted guidelines such as those published by the New England Journal of Medicine.[4] This disparity has resulted in inconsistent application of brain death criteria in Canada, the United States[5] and internationally.[6] Furthermore, the care of critically brain-injured patients may involve various medical practitioners including emergency physicians, adult and pediatric critical care specialists including anesthesiologists, and neurosurgeons, all of whom may apply different guidelines in evaluating for brain death.

History of the brain death concept

Rabbi Moses Maimonides was the first to suggest that the brain was of primary importance in sustaining life when he noted that decapitated individuals would invariably die. Prior to the introduction of mechanical ventilators in the mid 20th century and the evolution of resuscitative measures, a non-brain or circulatory formulation was used to determine death. Newer medical technologies resulted in the ability to artificially maintain patients with severe brain injury long after brain function ceased to exist.

In a seminal work published in 1959, Mollaret and Goulon[7] coined the term "coma dépassé" meaning "a state beyond coma", which described 23 cases in which loss of consciousness, brain stem reflexes, and spontaneous respiration was associated with absent encephalographic activity. While the initial intent of this work was to describe the futility of care in such cases, the subsequent introduction of organ transplantation later led to an inexorable linking of the issues of brain death, organ procurement, and transplantation which has continued into current medical practice.

In 1968, the ad hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death undertook to define irreversible coma and brain death.[8] The committee deliberations focused on a whole-brain formulation to define brain death. To this day, the whole-brain formulation serves as the foundation of the brain death concept in the United States.

In the 1970s Mohandas and Chou emphasized the importance of irreversible loss of brainstem function in brain death.[9] The importance of brainstem function then became the focus of a published statement by the Conference of Medical Royal Colleges and Their Faculties in the United Kingdom (UK) in 1976.[10] Subsequently championed by Pallis and Harley, the brainstem formulation of brain death was formally adopted in the UK in 1995.[11] Thereafter, UK physicians abandoned the use of ancillary diagnostic testing provided that a well-established etiology for brain death was identified, and that conditions known to mimic absent brainstem function, such as hypothermia and pharmacologic intoxication, were excluded.

In 1981 the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research[12] reaffirmed the application of a whole-brain definition for brain death in the USA stating, "This view gives the brain primacy not merely as the sponsor of consciousness (since even unconscious persons may be alive), but also as the complex organizer and regulator of bodily functions. Only the brain can direct the entire organism." Consistent with the President's Commission, Bernat *et al.*[13] also defined death as "the permanent cessation of functioning of the organism as a whole". However, it is well recognized that anterior pituitary neuroendocrine function may be preserved in patients who otherwise fulfill all clinical criteria for brain death.[14]

The use of ancillary diagnostic testing in the determination of brain death was addressed in the 1981 recommendations of the President's Commission. To this day many international guidelines mandate ancillary diagnostic testing to establish brain death.[6] The President's Commission also recommended that patients suffering from hypoxic brain injury should be

TABLE I Comparison of adult guidelines for brain death determination according to CNCG[1] and Wijdicks EFM[2]

Criterion	*CNCG guideline[1]*	*Wijdicks EFM guideline[2]*
Coma	+	+
Absent motor response	+	+
Absent pupillary response to light	+	+
Absent corneal reflex	+	+
Absent caloric response	+	+
Absent gag reflex	+	+
Absent cough with tracheal suctioning	+	+
Absent sucking reflex	+	+
Absent rooting reflex	+	+
Absent respiration with $PaCO_2$ = 60 mmHg	+	+
	As determined by arterial blood gas or apnea duration > 8 to 10 min	**or** $PaCO_2$ 20 mmHg above normal baseline value

+Ccriteria present; CNCG = Canadian Neurocritical Care Group.
1 Adapted from: *Canadian Neurocritical Care Group*. Guidelines for the diagnosis of death. Can J Neurol Sci 1999; 26: 64–6.
2 Adapted from: *Wijdicks EFM*. The diagnosis of brain death. N Engl J Med 2001; 344: 1216.

TABLE II Comparison of pediatric guidelines for brain death determination according to CNCG[1] and Wijdicks EFM[2]

Criterion	*CNCG guideline[1]*	*Wijdicks EFM guideline[2]*
Pediatric brain death clinical criteria	Adult clinical criteria applicable when post-conceptual age > 52 weeks	
Age related pediatric guidelines	Newborns > 38 weeks gestation and infants 7 days to 2 months of age – clinical examination and radionuclide brain flow study	Interval between examinations Term to 2 months old – 48 hr ➢ > 2 months to 1 yr old – 24 hr ➢ > 1 yr old to < 18 yr old – 12 hr ➢ ≥ 18 yr old – interval optional
	> 2 months to 1 yr old – two clinical examinations and two EEG separated by at least 24 hr; repeat examination and EEG can be eliminated by a positive radionuclide brain flow study.	Confirmatory testing† Term to 2 months old – 2 confirmatory tests ➢ > 2 months to 1 yr old – 1 confirmatory test ➢ > 1 yr old to < 18 yr old – optional ➢ ≥ 18 yr old -optional
	> 1 yr – observation period of at least 12 hr recommended except in presence of hypoxic ischemic encephalopathy where 24 hr observation is recommended.	
	Application of clinical criteria to preterm infants is uncertain; ancillary testing is required to substantiate brain death.	

EEG = electroencephalography . †Confirmatory tests may include cerebral angiography, EEG, transcranial Doppler ultrasonography, or cerebral scintigraphy. Testing may be legally required in some jurisdictions.
1 Adapted from: *Canadian Neurocritical Care Group*. Guidelines for the diagnosis of death. Can J Neurol Sci 1999; 26: 64–6.
2 Adapted from: *Wijdicks EFM*. The diagnosis of brain death. N Engl J Med 2001; 344: 1216.

observed for no less than 24 hr prior to determination of brain death. A subsequent brain death guideline published in 1995 by the American Academy of Neurology[15] reaffirmed that the diagnosis of brain death should be based upon clinical assessment and clarified the application of ancillary testing in those cases where confounding factors such as hypothermia existed.

Canadian perspectives on brain death

The first published Canadian guidelines for brain death determination appeared in 1987 in the Canadian Medical Association Journal.[3] In 1999 these guidelines were superceded by the Canadian Neurocritical Care Group (CNCG) guidelines[1] which were similar to those prepared by the American Academy of Neurology in 1995.

The CNCG guidelines are summarized and contrasted to those published by Wijdicks in 2001[4] (Tables I and II). Both require that an established etiology

capable of causing brain death be identified and that reversible conditions mimicking brain death be either excluded or reversed. They differ primarily in two key areas: the interval time between successive clinical evaluations and the application of ancillary diagnostic testing in the newborn and pediatric patients.

It is generally recommended that the brain-dead patient be reassessed within an appropriate time interval, although there is marked variability in the recommended time interval between examinations. The second evaluation may serve to ensure that absence of brain function is persistent and may also reduce the risk of error based upon a single examination. The CNCG guidelines recommend a 24-hr period of observation in those patients suffering from hypoxic-ischemic brain injury in a manner consistent with many other international guidelines.

Whole-brain death *vs* bainstem death

In the United States, the UDDA codifies the whole-brain formulation of brain death in stating that "an individual who has sustained irreversible cessation of all functions of the entire brain, including the brainstem, is dead." This formulation is the one most commonly applied worldwide, and forms the foundation for legal codification in many Western nations. A notable exception exists in the United Kingdom where the brainstem formulation of brain death is applied.[11]

The whole-brain formulation is characterized by irreversible loss of function of both the cerebral hemispheres and the brainstem. An intact brainstem is integral to the preservation of most regulatory and homeostatic mechanisms while the reticular formation, thalamus, and cerebral hemispheres all play roles in the preservation of consciousness. Global disruption of these structures forms the basis for whole-brain death.

It has been argued that laboratory evidence of retained hypothalamic-pituitary activity is inconsistent with the whole-brain formulation of brain death.[16] Bernat[17] rejects laboratory evidence of cellular function, arguing that isolated cellular activity may persist in the absence of clinical signs of brainstem activity. Wijdicks provides a pathophysiologic explanation for preservation of hypophyseal-pituitary axis activity in brain death, noting that perfusion to these structures arises from extracranial vessels.[18] Continued cellular activity may be a manifestation of retained blood flow to these nests of cells despite total intracranial cerebral circulatory arrest.

Clinical evaluation of these structures in the context of brainstem death is identical to that used for the evaluation of whole-brain death. The brainstem formulation of brain death requires irreversible cessation of brainstem functioning and is based on the fact that the reticular formation forms the basis of consciousness and that the brainstem nuclei preserve regulatory and homeostatic mechanisms. Destruction of the brainstem and reticular formation should result in unconsciousness.[19] Nevertheless, others have argued against using the brainstem formulation because of the possibility of a "super locked-in syndrome" in which awareness might be retained in the absence of all other signs of brainstem activity.[19]

Controversies in neurological determination of brain death

Despite numerous publications addressing the issue of brain death, there is a paucity of evidence-based literature to support many current practices related to brain death determination.

Physician expertise

While some guidelines and statutes specify the qualifications of those engaging in brain death determination, many do not. There is no evidence in the literature to recommend any one specialty over another. Critical care physicians, neuroscience specialists, anesthesiologists, trauma surgeons and emergency medicine physicians are frequently involved in the care of critically brain injured patients. Appropriate training supplemented by substantial clinical experience may be more important than the specialization of the attending physician. Many guidelines explicitly exclude those physicians involved in organ transplantation from brain death determination processes, as mandated by existing law in all Canadian provinces and territories.

Clinical criteria

Clinical assessment to determine brain death is remarkably similar in all guidelines (Tables I and II). Where full examination is restricted by the nature of the injuries, it is generally, but not uniformly, recommended that ancillary diagnostic testing be performed. All guidelines require an absence of centrally mediated response to pain. A proportion of patients may continue to display some reflex spinal activity which can confuse the casual observer or the inexperienced clinician.[16] Observed spinal reflex activity may range from subtle twitches to the more complex "Lazarus sign".[26] Persistence of these reflexes is compatible with brain death as confirmed by EEG testing or absence of cerebral blood flow.

There are subtle differences in many guidelines regarding assessment of pupillary response to light and

degree of dilatation, but no scientific basis for these differences has been clearly identified. Most guidelines make no mention of the oculocephalic or doll's eye reflex. Despite this, Pallis and Harley[11] recommend the inclusion of doll's eye response even though it is not required by the United Kingdom code for brain death determination. Wijdicks does not include the oculocephalic reflex in his guidelines, arguing that this reflex lacks sensitivity in adult brain injured patients.[18] Ashwal recommends that the reflex be evaluated and documented in neonates and infants in whom the vestibulo-ocular reflex may be more difficult to determine.[21]

Determination of persistent apnea is required in all guidelines although specific endpoints for evaluation are inconsistent. In less technically advanced nations apnea determined by ventilator disconnection may be sufficient.[6] However, most Western guidelines require documentation of apneic threshold as determined by arterial blood gas analysis, while in the United Kingdom a threshold $PaCO_2 \geq 50$ mm Hg is required. Most North American guidelines recommend an apneic threshold $PaCO_2 \geq 60$ mm. Hg. Some guidelines also require documentation of an acidemic pH < 7.28. An evidence base for these thresholds could not be identified.

Subsequent clinical examinations and time intervals

A second clinical evaluation has been a feature of guidelines dating back to the original Harvard criteria for brain death. While the origin of this second examination has become obscured by history, it was presumably introduced to minimize the likelihood of technical errors in examination.

Most clinical guidelines require two clinical examinations within a predetermined time interval depending upon the etiology of brain injury. Most commonly, it is recommended that a 24-hr observation period between examinations be observed in hypoxic-ischemic brain injury. Guidelines, however, tend to be less specific regarding appropriate interval times in all other clinical circumstances. Interval waiting times have progressively diminished since the earliest guidelines of the ad hoc Committee of the Harvard Medical School. Some guidelines such as those developed by the Australia and New Zealand Intensive Care Society (ANZICS)[20] mandate that two different physicians determine brain death when organ transplantation is being considered; most do not. More commonly, a single physician may perform both clinical examinations. There is no scientific evidence to support any of these positions in the medical literature.

Age-specific pediatric NDD guidelines

There is little scientific basis for published age-related guidelines (Table II). In spite of this, virtually every guideline acknowledges that protocol changes in evaluating neonates and infants are required. Most authorities agree that adult clinical criteria may be applied in children with a post-conceptual age of 52 weeks. However, clinical examination alone is generally thought to be insufficient in children less than one year of age. Ashwal provides recommendations regarding examination interval times based upon patient age.[21] These recommendations are strikingly similar to the recommendations of the American Academy of Pediatrics Task Force on Brain Death in Children.[23]

Confounding factors

It is well recognized that hypothermia, defined as core temperature < 32°C, induces hyporeflexia and that at temperatures < 28°C areflexia may ensue.[22] Despite this fact, level of consciousness and core temperature are poorly correlated.[18] Many guidelines include specific core temperature thresholds for clinical determination of brain death, but recommended thresholds range from 32.2°C to 36.0°C without clear evidence base for any of these limits.

Brain death determination in the presence of recognized therapeutic or self-administered drug intoxication requires attention to the pharmacokinetic profile of the identified agent.[18] Where the identity of the administered agent is unknown, drug screening should be considered, and ancillary testing to confirm cerebral circulatory arrest is recommended.

Ancillary testing

While brain death determination is based upon clinical history and examination, confounding clinical conditions frequently dictate the need for evaluation beyond the minimum clinical requirements for brain death determination. Where all criteria for brain death are met, there is no need to consider ancillary diagnostic testing. Unfortunately, traumatic injuries of the eyes and ears frequently co-exist with brain injury and metabolic disturbances may be identified in brain injured patients.

Published guidelines regarding ancillary testing typically recommend assessment of whole brain blood flow or electroencephalographic activity (EEG). The two currently validated diagnostic tests capable of identifying complete cerebral circulatory arrest are cerebral angiography and Tc-99m hexamethylpropylene-amine oxime (Tc-HMPAO) radionuclide angiography.[24,25] The EEG is still required in some

jurisdictions, especially in the pediatric population. EEG examination is limited by an inability to detect activity in deep brain structures and electrical interference in the intensive care environment when high gain examinations are performed. This testing may also be adversely affected by conditions such as hypothermia and pharmacotherapeutic agents used in the management of brain injured patients.

Legal time of death

From a legal perspective, the timing of death has significant implications. For example, probate proceedings may be triggered, and claims for wrongful death and criminal prosecutions may be initiated upon declaration of brain death.

The medical literature fails to address the issue of timing of legal death in the case of brain dead patients where two examinations for brain death are required in most jurisdictions. Following the first determination of brain death, Pallis states that the patient becomes a "ventilated cadaver".[11] Although Wijdicks does not address this specific issue, he acknowledges that, in experienced hands, the second examination for brain death is invariably consistent with the first, and that an apnea test need not be repeated during the second evaluation.[18] From these statements, it is reasonable to conclude that the declaration of death could be established at the time of the first brain death examination.

Conclusions

Because of existing variabilities and inconsistencies in neurological determination of death, it is necessary to generate and disseminate uniform criteria. Adequate technical training and clinical experience with NDD are central considerations related to the appropriate evaluation of brain injury cases.

A number of clinical guidelines for NDD which share many common features have been published in the literature. However, variability and inconsistency within these guidelines does exist, particularly in regard to the thresholds applied to diagnostic tests and requirements for ancillary testing. These discrepancies appear to reflect the lack of scientific evidence in the literature and selected thresholds may represent the collaborative decision by various bodies and organizations developing guidelines. In a similar vein, consensus building may lead to a more widely accepted guideline for NDD in Canada, with more uniform application of criteria nationwide.

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