Brain death/death by neurologic criteria determination: an update

Gea Drost[a], *Anthony R. Absalom*[b] *and Michael A. Kuiper*[c,d]

Purpose of review
Brain death, also known as death by neurologic criteria (DNC), is a well-established concept. In this article, we present a short history of the concept and give an overview of recent changes and a practical update on diagnosis and definitions of brain death/DNC. Unresolved issues will be discussed.

Recent findings
There is variability in brain death/DNC determination worldwide. In recent years, successful attempts have been made to harmonize these criteria and, consequently, to improve public trust in the process and diagnosis. An international multidisciplinary collaboration has been created and it has published minimum criteria, provided guidance for professionals and encouragement to revise or develop guidelines on brain death/DNC worldwide.

Summary
There are two sets of criteria for declaration of death. First, if there is neither cardiac output nor respiratory effort, then cardiopulmonary criteria are used. Second, if both the cerebrum and brainstem have completely and permanently lost all functions, and there is a persistent coma, absent brainstem reflexes and no spontaneous respiratory effort, death can be declared on the basis of brain death/DNC. Although attempts to formulate uniform criteria are ongoing, consensus has been reached on the minimum criteria. Some inconsistencies and questions remain.

Keywords
brain death, death by neurologic criteria, diagnostic criteria

INTRODUCTION

Brain death, presently more precisely termed 'death by neurologic criteria' (DNC), is defined as the complete and permanent loss of all functions of the brain, including those of the brainstem, expressed as an unresponsive coma with loss of brainstem reflexes, and the ability to breathe spontaneously [1▪▪]. It is accepted as evidence of death in many (mainly Western) countries, but not worldwide [2,3▪]. 'Permanent' as referred to in this definition means that the loss of function cannot be regained spontaneously nor will it be restored through intervention [4]. Because the term DNC describes the mode of determining death, it is considered more appropriate than the term brain death. The term brain death can cause particular confusion because it can be taken to imply that all brain cells are dead whereas this is not necessarily a requirement for the diagnosis [5].

Although it is now more than fifty years since the introduction of the concept, there remain essential differences among countries and jurisdictions in their understanding and definition of the concept of brain death/DNC [3▪,6].

In most countries the failure of the function of the whole brain is the starting point and this 'whole brain death concept,' is used for defining brain death/DNC. In other countries, such as the UK, the 'brain stem death concept' is the starting point [3▪,7]. Brain stem death is defined as the combined clinical finding of coma, apnea, and loss of all tested

[a]University of Groningen, Department of Neurology and Neurosurgery, University Medical Center Groningen, Groningen, The Netherlands, [b]University of Groningen, Department of Anesthesiology, University Medical Center Groningen, Groningen, The Netherlands, [c]Department of Intensive Care, Medical Center Leeuwarden, Leeuwarden and [d]Dutch Transplant Foundation, Leiden, The Netherlands

Correspondence to Gea Drost, MD, PhD, Neurologist and Clinical Neurophysiologist, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9700HB Groningen, The Netherlands.
Tel: +31 50 361 3968/3612837; fax: +31503611715;
e-mail: g.drost@umcg.nl

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KEY POINTS

- There is variability in brain death/DNC determination worldwide. Worldwide consultation and cooperation lead to harmonization of brain death/DNC guidelines.
- An operational definition of brain death/DNC is the complete and permanent loss of brain function as defined by an unresponsive coma with loss of capacity for consciousness, brainstem reflexes, and the ability to breathe spontaneously.
- Most countries adhere to the 'whole brain death concept' for defining BD/DNC. In some other countries, most notably the UK, the 'brain stem death concept' is used.
- This review gives a practical update on the different steps necessary to determine brain death/DNC, with emphasis on recognizing diagnostic confounders.
- The determination of death, and thus brain death/DNC, is not merely a scientific question to be answered by physicians and encompasses philosophical, religious, judicial, and cultural aspects.

brainstem reflexes [8,9]. Operationally, these two concepts are similar: both require loss of consciousness and brainstem reflexes, as well as respiratory reflexes. The main objection to the brain stem concept is the risk that patients with an extreme version of a locked-in syndrome could be considered brain dead. If the brainstem is injured, supratentorial structures can still function if the reticular activating system function can be restored. This has consequences for the diagnostic criteria for brain death/DNC determination. After all, if there is an infratentorial or brainstem lesion and the whole brain death concept is valid, ancillary tests are needed to demonstrate that there is no longer any cortical function [10]. Recent publications recommend that the terms 'whole brain death' and 'brainstem death' should no longer be used and should be replaced by brain death/DNC [1▪▪,3▪,11].

Epidemiological studies have estimated that in 2% of all in-hospital adult deaths in Europe and the USA the mode of death is declared to be brain death/DNC [12].

Although the brain death/DNC concept is widely accepted, there is not yet a uniform worldwide protocol defining how brain death/DNC should be determined. In recent years some important publications have aimed to reduce the heterogeneity in methods of diagnosing brain death/DNC. In 2020, the largest and most detailed assessment of protocols for brain death/DNC determination in 83 countries was published, and clearly showed considerable variability worldwide [3▪]. In response to this article, several critical remarks were made on the diagnostic standards, and recommendations were made on how to improve these [13]. Because of these inconsistencies, the World Brain Death Project (WBDP) was initiated in the USA. This resulted in publication of an international consensus statement on brain death/DNC diagnosis [1▪▪] in which it became clear that despite the differences in brain death/DNC determination protocols, practices around the world are quite similar.

HISTORY

For centuries, different criteria have been used to define the border between life and death and these have been the subject of endless discussion and study. In 1628 Harvey published his book ''De Motu Cordis'', in which he described the central role of the heart in the circulation of the blood and hence life. Thereafter a cardiorespiratory standard for establishing death became dominant. When artificial ventilators were introduced in the 1950's, things became more complicated: can a patient without demonstrable brain function who is mechanically ventilated and has a beating heart be considered to be a living person [14]? In 1968 an ad hoc committee at Harvard Medical School arrived at what would later be seen as an initial definition of brain death [15]. It is important to acknowledge that brain death/DNC is not just a theoretical construct with the exclusive purpose of facilitating organ donation. While the paper made organ donation possible, the primary goal was aimed to end the practice of continuation of measures that had no value for the patient with irreversible brain damage [15]. In the 1970s, most countries accepted death criteria that referred to the cessation of brain functions. This resulted in the publication of criteria, guidelines, and protocols for the diagnosis of brain death/DNC. Many revisions have been made and have led to differences between and even within countries [3▪,10,16]. The American Academy of Neurology (AAN) published their latest revisions of a standard for brain death/DNC for adults in 2010 [17]. The questions addressed by the Harvard ad hoc committee are still vivid, as is demonstrated in many recent articles about ethical issues concerning brain death/DNC [18–20].

CURRENT DIAGNOSTIC CRITERIA OF BRAIN DEATH/DEATH BY NEUROLOGIC CRITERIA

Currently, there is a global consensus on brain death criteria and brain death /death by neurologic criteria determination that rests on the following pillars: the

prerequisites; a clinical neurological examination to establish the presence of coma and absence of brainstem reflexes; and the apnea test [14]. There is no consensus on ancillary testing [1▪▪]. The variation between countries in the ancillary testing requirements is most often based on local resources and preferences.

PHASE 1. PREREQUISITES FOR BRAIN DEATH/DNC

In order to establish brain death/DNC, the patient should have: a neurologic diagnosis that is known to lead to complete and irreversible loss of all brain function. No conditions that may confound the clinical examination and diseases that may mimic brain death/DNC. Be aware that most errors in the diagnosis of brain death/DNC occur during this phase [21]. Coma without a known cause is incompatible with a diagnosis of brain death/DNC.

Established neurological diagnosis

During this phase, a determination of patient's history is necessary, and a physical examination to obtain a number of basic diagnostic data in order to exclude other causes of unconsciousness. This general examination should also help to determine whether the brain injury is fatal, what caused it and whether there are no treatment options. Severe brain damage with irreversible loss of all clinical brain functions does not automatically mean that a patient will meet the brain death/DNC criteria. In patients who have suffered a devastating brain injury, commonly due to trauma, bleeding in the brain, stroke, or loss of blood flow to the brain after, for example, cardiac arrest, a diagnosis of brain death/DNC can only be made in some cases [12]. If no organ donation will follow, in a proportion of these patients, withdrawal of life sustaining treatment (WLST) can occur on medical grounds without the requirement for a determination of brain death/DNC.

Once the diagnosis is clear, it must be proven that the brain injury is irreversible, meaning that loss of function is complete and constant over time and cannot be reversed. There is no consensus concerning the timing of observations [11]. However, if a patient is admitted after return of spontaneous circulation following cardiopulmonary resuscitation, a delay of at least 24 h is recommended [11].

Confounders of brain death/death by neurologic criteria

Presence of a clear diagnosis that can lead to brain death/DNC is necessary because reversible syndromes can cause absence of brainstem reflexes and spontaneous respiratory effort. Examples of problems that can cause absent brainstem reflexes and mimic the neurological picture of brain death/DNC include fulminant 'polyneuritis' (Guillain-Barré syndrome), brainstem encephalitis, CMV-encephalitis, botulism, high cervical cord injuries, snake bites and rabies [21]. Conditions such as hypothyroidism, hypothermia, diffuse leptomeningeal carcinomatosis, and vasculitis of the central and peripheral nervous system also need to be ruled out, as they can also lead to reversible symptoms mimicking brain death /DNC [21].

Even if there is a known cause that can potentially lead to brain death /DNC, it is still necessary to ensure that there are no other confounding factors, which can be reversible and influence the condition of the patient. Grzonka *et al.* found 45 cases mimicking brain death /DNC and 19 confounders [21]. Full recovery rates in these cases are three times higher than overall mortality. The importance of precise and accurate clinical workup to ensure a reliable diagnosis or exclusion of suspected brain death /DNC is clear. First, probably the most important (and difficult) confounders are intoxications caused by medications or drugs that suppress the central nervous system [22]. The drugs most mentioned in the literature are antiseizure drugs (carbamazepine, pentobarbital, and valproic acid), Baclofen, Bupropion and Ethylene glycol. Other substances mentioned include amitriptyline, lidocaine, and organophosphates such as those used in nerve gases [21,22]. A list of medications that could lead to a false-positive declaration of brain death /DNC can be found in the paper of Lewis and Kirschen [6].

Especially in India, snake envenomation can be found to resemble brain death/DNC [22]. Baclofen was the second most frequent agent mentioned in this review. Loss of brainstem reflexes can occur with a dose as low as 450 mg [23], but mostly it was 1 g or more. Toxicology results should therefore be considered before brain death/DNC diagnosis, especially when neuroimaging shows normal results.

The second group of confounders comprises of medications that yield pharmacologic paralysis, such as muscle relaxants, or medications that can cause coma like anesthetic drugs (vide infra).

Other factors which can be a confounder in the diagnosis of brain death/DNC are hypotension, hypothermia or hypoglycemia. Therefore, adults should have a systolic pressure $\geq$ 100 mmHg or mean arterial pressure $\geq$ 60mmHg before neurological examination to diagnose brain death/DNC can start [1▪▪,24]. Temperature must be $\geq$36 ^{0}C according to the AAN 2010 and WBDP standards, and >35^{0}C according to the SCCM/AAP/central nervous system (CNS) standard [1▪▪,17].

There is no scientific evidence for lower and upper limits for pH, and concentrations of electrolyte and hormones before brain death/DNC evaluation. Nonetheless, in some countries clear cut-off values are provided. The AAN 2010, 2011 SCCM/AAP/CNS and WBDP standards recommend exclusion of 'severe' derangements [1▪▪,3▪,17,25].

Drug-induced impairment of consciousness

Although there is no clear evidence concerning acceptable drug concentration thresholds, most protocols state that the physical examination should not be performed until at least 5 half-lives have passed following administration of CNS depressant medications [1▪▪,6,17,25]. Drug-induced CNS depression can make the assessment of the neurological examination, the EEG, and the apnea test unreliable [1▪▪,6,17]. Brain death diagnostic procedures may only be initiated when there is agreement among the clinicians involved in the care of the patient, that drug-induced CNS depression is no longer present, so that it can no longer confound the results of the neurological examination and the apnea test. The question is then, when is there no risk of residual drug-induced CNS depression? In some countries further criteria have been drawn up for this based on multiples of the half-lives of commonly used drugs [1▪▪,26]. In the recommendations of the WBDP, the statements about the influence of CNS depressing medications including toxins is stated as follows: *I. use of a toxicology screen if there is concern for a toxic exposure II. Serially measurements of drug levels to ensure that they do not exceed the therapeutic range, and, even if within the therapeutic range, are not thought to confound the clinical examination or III. Waiting 5 multiples of the elimination half-lives before an evaluation for BD/DNC is made (assuming normal hepatic and kidney function), or VI. Performing ancillary testing in addition to the complete clinical examination and apnea test if there is concern about prolonged or unknown drug elimination* [1▪▪]. This last statement is not valid for all countries though. In the Netherlands, the BD/DNC protocol demands an apnea test, and therefore CNS depression always needs to be ruled out. This is because if there is concern about the validity of the neurological examination and/or the apnea test, two main pillars of the BD/DNC determination are not solid or are even absent.

PHASE 2. CLINICAL NEUROLOGICAL EXAMINATION IN BRAIN DEATH/DNC

After the diagnosis has been clearly identified, and after exclusion of reversible conditions, clinical testing can start. This is best done after an observation period, because it must be proven that the loss of function is complete and constant over time. As a general rule, as with any phase, if there is any doubt about reversibility, clinicians should delay performance of testing to exclude any doubt [1▪▪]. The clinical determination of brain death/DNC includes an assessment for coma and an evaluation for loss of brainstem functions [1▪▪,6,11]. The following tests must be performed according to the WBDP and AAN criteria [1▪▪,17,26]: There is no brain-mediated motor response to noxious stimulation of the limbs. The pupils are fixed in a midsize or dilated position and are unreactive to light. Corneal reflexes are absent. Oculocephalic and oculovestibular reflexes are absent. There is no facial movement to noxious stimulation in the cranial nerve dermatomes. The gag reflex is absent to bilateral posterior pharyngeal stimulation. There is no cough reflex in response to deep tracheal suctioning [1▪▪,11,17,27]. Spears *et al.* published detailed guidance on how to perform these tests [11]. In order to determine brain death/DNC, the absence of brainstem function is an absolute requisite and, especially since it is based on clinical neurological examination, an essential phase in determining brain death/DNC. If, for example due to severe trauma or swelling of the face, testing of a portion of brainstem reflexes is not possible, and the other tests are compatible with brain death/DNC, ancillary testing should be carried out [1▪▪,26]. The minimum number of examinations for brain death/DNC determination varies [3▪]. In adults, no data provide evidence that multiple physical examinations are more reliable than a single examination for determination of brain death/DNC [28].

PHASE 3. THE APNEA TEST

In almost all protocols worldwide, apnea testing is part of the brain death/DNC protocol [28]. It is an essential element in determination of the absence of brainstem function. Because there is concern that the apnea test may elevate intracranial pressure or induce hypoxia and lead to arrhythmias, it is recommended that the apnea test is conducted after the rest of the clinical examination and ancillary testing has been completed and found to be consistent with brain death/DNC. The goal of the apnea testing is to maximally stimulate the medullary respiratory centres to trigger breathing.

One can argue that demonstration of absent spontaneous respiratory effort provides convincing proof that a person is deceased [1▪▪,17,27,29]. In general, it is not possible to perform the apnea test if there is a high cervical lesion of the spinal cord, or any other condition in which a patient is not able to

breath unassisted. If performed, there is a need to provide proof of an elevated carbon dioxide and, as proposed in the paper by Greer *et al.*, of a decreased pH [1▪▪]. Most often the apnea test is performed after sufficient preoxygenation, most often with 100% O_2, for at least 5, but more often 10 min. Before the start of the apnea test, arterial blood gas analysis is performed to measure pH, $PaCO_2$ and PaO_2, to ensure that they are in the normal range before the start of the apnea test. In patients with known severe chronic obstructive pulmonary disease, a value of 'normal' pCO_2 for that patient needs to be established.

The apnea test can be performed by disconnecting the endotracheal tube from the ventilator and supplying oxygen by T-piece, catheter, or by using a CPAP system. The responsible medical professional (s) need to observe the chest wall for spontaneous respiratory efforts. Be aware of the risk of artefactual triggering of ventilation when the patient is not disconnected from the ventilator (particularly when the ventilatory is programmed to provide pressure support triggered by pressure changes in the breathing circuit)! Even very light impulses, such as those caused by changes in intra-thoracic pressure due to the heartbeat, can trigger mechanical breaths from modern ventilators, and back and forth movement of tiny amounts of fluids in the ventilator tubing can sustain the illusion of breathing. For these reasons it is good practice to disconnect the endotracheal tube from the breathing circuit of the ventilator. In patients with a lung disorder such as aspiration or contusion, this may not be possible due to impending hypoxia during the apnea test.

The 2010 AAN standard demands a target $PaCO_2$ $\geq$60 mm Hg *or* $\geq$20 mm Hg above baseline and the 2011 SCCM/AAP/CNS standard demands a target $PaCO_2$ of $\geq$60 mm Hg *and* an increase of $\geq$20 mm Hg above the baseline value [6]. Reasons to abort the apnea test are the occurrence of spontaneous breaths, a decrease of the systolic blood pressure $<$100 mm Hg or mean arterial pressure $<$60 mm Hg, sustained arterial oxygen desaturation $<$85%, and unstable arrhythmias or hemodynamic instability. A special challenge is the situation of patients who are undergoing extracorporeal membrane oxygenation or any other form of extracorporeal support, and in whom brain death/DNC needs to be established. In general, the same principles apply as in the normal procedure for apnea testing. For further details refer to supplement 7 of the Determination of Brain Death/Death by Neurologic Criteria by Greer *et al.* [1▪▪].

PHASE 4. ANCILLARY TESTING

If a patient can be determined to fulfil the criteria for brain death/DNC, ancillary testing is not needed in most countries [8,26]. The purpose of ancillary testing is to demonstrate that cortical function is no longer present. This can be done by evaluating the loss of intracranial blood flow or the loss of electrical cerebral activity.

If a portion of the clinical examination or the apnea test cannot be completed, unresolvable confounding conditions are present, or uncertainty regarding interpretation or if possible spinally mediated movements exist, ancillary testing is needed [1▪▪,17]. There are advantages and disadvantages to all ancillary tests [30]. The following ancillary tests are used as additional tests to determine brain death/DNC: 1neurophysiological function tests: electroencephalography and evoked potentials and tests to assess for presence or absence of intracranial blood flow such as 4-vessel conventional cerebral angiography, computed tomographic angiography [29,30], radionuclide studies using diffusible radiopharmaceuticals [1▪▪], and transcranial Doppler ultrasonography. There is discussion if MRA can be used as an ancillary test in brain death/DNC determination, and the results of further research into the sensitivity and specificity are awaited. For further details we refer to table 1 and table 2 and Supplement 5 of Greer *et al.* [1▪▪].

If ancillary testing is performed and brain blood flow, or electrical activity on the EEG, is demonstrated, then brain death/DNC cannot be declared at that time.

DISCUSSION

Although there are worldwide differences in the protocols how to determine brain death /DNC, there are, as previously indicated, many similarities especially in the implementation. Additionally, while consensus on the protocols on brain death /DNC determination is certainly important, ultimately this is not just a scientific question for medical experts. Besides the consistency in diagnostic criteria, it should be kept in mind that the determination of death is not merely a scientific question to be answered by physicians. This question goes beyond consistency of standards, encompassing philosophical, religious, judicial, and cultural aspects [31,18,19]. Moreover, it is questionable whether a uniform global protocol on brain death/DNC is desirable and feasible. Given the limited resource availability, as well as religious, societal, and legislative differences, a more local adaptation of guidelines for brain death/DNC determination may be desirable [1▪▪,32]. Future research also needs to focus on the cross-cultural differences on fundamental questions about the concept of brain death/DNC [13,32,33].

Even if one shares the view that brain death/DNC can be defined, there is no consensus on whether the diagnosis requires evidence of death of the whole brain or only of the brainstem, as is the case in the UK [8,34]. If the 'whole brain death concept' is accepted, then ancillary testing will need to be performed, for example in cases in which brain death/DNC is determined in patients with infratentorial or brainstem lesions to exclude supratentorial brain function [1▪▪,28,29].

All the recent new insights made it clear that laws about brain death/DNC needed to be adjusted [35]. In the USA this meant that the 1981 Uniform Determination of Death Act (UDDA), the legal standard for the determination of brain death/DNC, has to change forty years after its inception [35–38]. Furthermore, if there is to be more uniformity in the world regarding the criteria for brain death/DNC determination, there will have to be development and validation of clinical neurological research, and application of the findings to those large parts of the world that do not have access to the advanced technology necessary for neuroimaging and ancillary testing.

CONCLUSION

Recent international consultation and cooperation has led to harmonization of guidelines for diagnosis of brain death/DNC. There should be a known cause of injury and coma, and potential confounding conditions should have been excluded. A broadly accepted definition of brain death/DNC is the complete and permanent loss of brain function as defined by unresponsive coma with loss of capacity for consciousness, and absence of brainstem reflexes and spontaneous respiratory. Ancillary testing to demonstrate absence of cerebral blood flow and/or cerebral electrical activity is not required in most countries.

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- ▪ of special interest
- ▪▪ of outstanding interest

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