

REVIEW

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# Brain death: a review

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## Abstract

**Background** To date, the recognized medical criteria for BD/DNC (brain death/death according to neurological criteria) in the USA (United States of America) are the 2010 AAN (American Academy of Neurology) standards for identification of the BD/DNC for adult age and the 2011 Society of Critical Care Medicine/Child Neurology Society/American Academy of Pediatrics standards for identification of BD/DNC in Pediatrics.

**Main body** Though the definition of death should be constant between clinicians, hospitals, and nations to endorse that whoever is considered dead somewhere will not be regarded as alive in another place. This provoked the construction of the worldwide *Brain Death Project* that declared a global agreement report on the BD/DNC which is accredited by 5 international federations and 27 medical professional communities from all over the world. This review defines the essential requirements of BD/DNC, its assessment (including apnea test) on a clinical basis, usage of additional examinations, and the arguments for its definition worldwide.

**Conclusion** A precise and unbiased methodology is necessary to issue error-free declarations of death by defining BD/DNC while considering local regulations and values. Practitioners must learn to be familiar with the current guidelines, and the contents of the WBDP (world Brain Death Project) standard, which announces an updated International Agreement Report on BD/DNC and certified by 5 International federations and 27 professional medical communities from all over the world.

**Keyword** Brain Death, Apnea test, Organ donations

## Introduction

Thanatology is known as the scientific study of death and the related practices, as well as the study of the requirements of the terminally ill and their families. The medico-legal dilemmas concerning the description of death are not new [10]. Cardiopulmonary or neurologically based criteria (conventionally termed brain death) can be used to declare the death of an individual. However, BD/DNC is recognized as a death in most parts of the world despite the unknown incidence of declaration. According to some studies, the USA (United States of America) and Europe used neurologically-based criteria to declare

2–12% and 20% of deaths in adults and children respectively [12, 23].

Though BD/DNC was stated less often than via cardiopulmonary-based criteria, neurologists need to be proficient in defining BD/DNC, to prohibit false-positive statements regarding whether a person is alive or dead. Additionally, the process of the declaration must be the same and reliable throughout hospitals, countries, and nations to guarantee that a person who is affirmed dead somewhere is not considered alive by others. The current review explores the history of BD/DNC, the scientific criteria for its identification, and some of the associated confronts [12, 30]. Additionally, it defines the essential requirements of brain death/death according to neurologically-based criteria BD/DNC, its assessment (including apnea test) on a clinical basis, usage of additional examinations, and the arguments for its definition in worldwide.

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## Brain death history

The majority of ancient nations recognized death as a simply determined empirical fact, not demanding additional elaboration. Brain death was for the first time designated by 2 French doctors, *Goulon* and *Mollaret*, and called “*coma depasse*” (a condition beyond coma). Also, they distinguished “*coma depasse*” from “*coma prolonged*,” which is nowadays labeled as the persistent vegetative state (PVS) [34]. Earlier in the 1950s, the hypothesis of BD/DNC has been presented in Europe after it was repeatedly observed that some people connected to ventilators because of severe brain injury and coma, got absent brainstem reflexes, and inability to breathe spontaneously. Later in the year 1968, the 1st medical standard for BD/DNC was introduced at *Harvard Medical School* via an interdisciplinary team. They defined brain death as a permanent coma state, while the victim was entirely unresponsive and unresponsive, with no reflexes or spontaneous respiratory attempts throughout 3 min of withdrawal from the ventilator [7]. Yet *Joseph Verheijde* and *colleagues* [21] claimed against the legitimacy of the Harvard standards for connecting human death with brain death. Additionally, they stated that the brain death concept does not interrupt somatic consolidative unity and synchronized biological working of a surviving individual. A few years later, others [33] advocated that patient should have recognized but irreversible intracranial lesion(s) besides permanent injury to the brain stem, besides that the conclusion of brain death must be an entirely clinical diagnosis. Hence, the evolving need for a definition of death with a social acceptance plus the recognition that the BD/DNC must be integrated into laws had created additional medical criteria for the BD/DNC in the following years. Additionally, transplantation projects with the necessity for viable organs dictated the re-assessment of the death concept [39, 52]. A standard for the BD/DNC in adult people was published in 1995 via the *American Academy of Neurology (AAN)* and then renovated in the year 2010 [54, 55]. Formerly in the year 1987, a BD/DNC standard in pediatrics was published by *The Task Force of BD determination in Children*, which was updated later in 2011 via *Child Neurology Society (CNS)*, *American Academy of Pediatrics (AAP)* and *Society of Critical Care Medicine (SCCM)* [35, 41]. Though the definition of death should be constant between clinicians and hospitals, and nations to certify that whoever is considered dead somewhere will not be regarded as alive in another place, discrepancy happens in the diagnostic criteria, clinical and apnea testing. This provoked the construction of the worldwide *Brain Death Project* (known as *WBDP*), that announced a worldwide agreement report on BD/DNC and was accredited by 5 international federations and

27 medical professional communities from all over the world [12, 27]. This is intended to be provided to professional medical associations and nations to promote their rules on BD/DNC while considering community regulations, and values; yet, it does not aim to substitute the domestic medical ethics. Therefore, in anticipation of the announcement of an updated recommendation for defining BD/DNC across all age groups from birth, the previously mentioned 2011 SCCM/AAP/CNS regulations and the 2010 AAN regulations remain the current recognized standards for BD/DNC in the USA [28, 43].

## Geo-political variability for brain death determination

The USA does not approve the brain-stem death alone. However, many other countries find the diagnosis of brain death or brainstem death uneventful enough to approve death in adults. Currently, only 70 countries approve the practice of BD/DNC for defining death. However, a worldwide consensus and uniform solid guidelines are mandatory to prevent discrepancies and variations in this regard [10]. Diagnosis of brain stem death needs no validation that entire brain neurological functions have stopped. Continuing functions must not be considered to point to any pattern of consciousness. Auxiliary tests are encouraged only in the existence of mystifying factors. However, those cases with the maintained electrical activity of the brain cortex or intracranial cerebral blood flow can be counted dead in states that employ a brain stem methodology, but not in those that only use a whole-brain death concept. The biological dying of the entire human individual cannot (and is not obligatory to) be confirmed during the brain death diagnosis. Whereas there is agreement that approval of absent brain stem reflexes is essential to the clinical diagnosis of brain death, there are extensive differences in the necessities for the performance of the apnea test. Less than 60% of authorities incorporate provoked hypercarbia to a certain level in their management. Others only order the suspension of mechanical ventilation for a distinct period or offer no direction for the performance of the apnea test. This is of great importance since the approval of apnea is vital to the declaration of brain death (either whole brain or only brain stem) and this is only guaranteed if acute hypercarbia level is adequate to excite the brain stem respiratory center [10, 19].

## Etiology

In all age categories, a known extracranial or intracranial etiology may be responsible for brain death which happens next to significant damage of the brain neuronal cells resulting in permanent coma (loss of consciousness), absent brainstem reflexes, and apnea [54]. After

exclusion of unusual situations such as drug poisoning, extreme electrolyte imbalance, and endocrinal disorders, many causes are defined and confirmed as an acute and permanent etiology for brain death. In adults, intracranial causes like head trauma or subarachnoid hemorrhage are commonly seen, while non-accidental trauma is a common cause in pediatrics. The commonly faced extracranial cause is cardiopulmonary arrest [8].

### Pathophysiology and histopathology

The pathophysiology of brain death is analogous irrespective of the cause. Tissue hypoxia leads to a continuous gush of excess edema (due to liberation of cytotoxic materials), elevated intracranial pressure (which in turn impairs more the brain tissue oxygenation), marked reduction of cerebral perfusion and brain herniation, or complete stop of cerebral blood flow and a subsequent brain tissue aseptic necrosis [24, 50]. It is noted that the mechanism of cerebral edema during hypoxia is the influx of sodium ions across a pre-existing electrochemical gradient due to ATP (adenosine triphosphate) depletion and a defect in the Na<sup>+</sup>-K<sup>+</sup>ATPase pump; Besides disrupting the blood–brain barrier (damaged by reactive oxygen species), it contributes to increased fluid leakage and brain edema [31]. Microscopic examination of the brain in the post-mortem stage tells variable grades of neural ischemic patterns. The most frequent parts of the brain to suffer from severe ischemic alteration are the cerebral hemispheres and basal ganglia, followed by the brain stem, and thalamus, respectively. Cerebellar autolysis can also be seen in many postmortems [32].

### Universal rules

The BD/DNC assessment must only be achieved by qualified experts who are skilled in providing medical service for cases with serious brain insults and got competent in family counseling and BD/DNC determination [12]. Although no contemporary official credentials are mandatory for BD/DNC determination, instructive programs must warrant learners are properly educated about this subject through simulations, teachings, close

observation, and contribution in the assessment of cases with serious cerebral damages Neurocritical Care Society provides also online training. Avoiding rush in BD/DNC evaluation, getting familiar with domestic laws and rules plus careful awareness and attention to details would prevent practitioners from false-positive statements concerning death declarations [12, 51].

### Requisites for identification of BD/DNC

The BD/DNC evaluation must be limited to unconscious apneic patients with concomitant loss of brainstem reflexes and the presence of an evident cause for permanent brain damage. Conditions that lead to BD/DNC as well as simulators are enumerated in Table 1 [12]. Practitioners need to confirm the absence of hypothermia (minimum accepted is  $\geq 36$  °C corresponding to the 2010 AAN and WBDP standards), hypotension (minimum accepted are systolic  $\geq 100$  mm Hg for adults and not less than 2 standard deviations below age-appropriate norms for pediatrics), or hypoglycemia even though brain damage mechanisms were identified [12, 35, 55].

Additionally, drugs with a known central nervous system depression or paralysis (e.g., Barbiturates and Antiepileptics) must be ensured to be entirely cleared or metabolized before BD/DNC assessment (at least five half-lives have passed following its administration). It is to be noted that extra time is provided in cases of hypothermia, severe obesity, and liver or renal impairment. Wherever the AAN recommendations are followed, and no violation attempted, there have been no reported brain death misdiagnosis -if any- in the literature [8, 57]. Practitioners are advised to extremely be cautious while picking up the time to apply an evaluation for BD/DNC since no established period of observation has been recognized till now. They should also take into consideration the mechanism of brain damage which may delay the recovery, neuroradiological results, laboratory data, arterial blood pressure, ICP (intracranial pressure), body temperature, age of patients, administered drugs, and related social circumstances. Exceptional situations should be in mind, such as the negligible effect of

**Table 1** Causes and simulators for BD/DNC

Conditions that lead to BD/DNC	Simulators for BD/DNC
Traumatic head injury	Upper Cervical Spinal Cord Trauma
Hypoxic-ischemic or hepatic encephalopathy	Snake Venom
Ischemic/hemorrhagic stroke	Botulism
Viral encephalitis	Rabies
Meningitis	Grave Guillain-Barré Syndrome
Acute hydrocephalus	

raised ICP/brain herniation in infants due to unclosed fontanels compared to older children harboring closed skulls. Additionally, the brain stem in infants is considerably resistant to hypoxic-ischemic events relative to other brain areas. This may explain the rise of spontaneous respiratory activity or brain stem reflexes sometime later following the subsidence of brain edema. Thus, an extension time for observation is recommended for young age pediatric patients [37].

### Clinical evaluation for BD/DNC

Clinical evaluation and diagnosis of brain death must be completed as follows: (1) confirmation of the etiology; (2) Exclusion of all reversible conditions that may simulate brain death. and, (3) identification of clinical hallmarks of brain death namely coma, absence of brainstem reflexes, and complete cessation of spontaneous breathing (apnea) [18]. A clinical assessment is accomplished to judge for loss of consciousness, complete paralysis of the face and limbs, and areflexia of the brainstem. Occasionally, this task may be prevented by several causes such as critical maxillofacial injuries, serious cord trauma, and advanced neuromuscular diseases. In such cases, ancillary tests are dictated, while noting that it is augmenting but not replacing clinical examination. To consider patients in a coma with no limb or facial motor response, it is essential to establish that they do not respond to touch, acoustic and visual stimuli and no brain-controlled movements after applying painful pressure/pinching to the face and in two other sites on each limb [35, 55]. Patients who exhibit clinical standards for BD/DNC, may also show several spinal-mediated reflexes (confirmed via ancillary testing to originate below the level of the brainstem) (Table 2) [12]. It is worth noting that the diagnosis of brainstem death in most countries is based on clinical diagnosis, which is considered satisfactory to verify the announcement of the death diagnosis due to its ease, reliability, and accuracy. Brain stem death is defined as a permanent nonfunctional condition of this nervous system structure, where all its signs of activity are gone [13].

Practitioners must explain to the patient's families that mechanical ventilation is not maintained to prevent

patient's death (because he has already died) but that the maintenance of ventilation is only for the survival of particular organs. After the clinical examination and apnea testing has been completed and it is still not clear whether the finding was cerebrally mediated or not, it is needed to confer an additional consultant or accomplish confirmatory testing. Regarding the 2010 AAN and WBDP standards, brainstem reflexes included the pupillary, oculocephalic, corneal, gag, oculovestibular, and cough reflexes [12, 55]. These reflexes are also involved in the 2011 SCCM/AAP/CNS standard except for the oculocephalic reflex. However, the WBDP and the 2011 standards asked to confirm the lack of rooting and sucking reflexes in young infants [12, 35].

With regard to the pupillary light reflex, the testing must be performed bilaterally, with an adequate close observation not less than one minute for the detection of what is called "slow response." The mid-sized or widely dilated fixed pupils are sure positive tests for brain death diagnosis. The absence of reaction to light (i.e., fixed pupils) rather than its dilatation is an essential diagnostic requirement since the sympathetic cervical pathways supplying the dilator pupillae muscle fibers are still functioning [40, 48]. It is to be noted that the same nerves are tested in the oculovestibular reflex as that for oculocephalic reflex and are, really, more sensitive. Therefore, in case of a recognized cervical spine injury, BD/DNC may still be declared clinically provided the oculovestibular reflex is proved to be missing [12]. Though wide variations across the world, the WBDP guidelines denote that at least one clinical assessment for an adult and two for pediatrics to declare BD/DNC, which is consistent with 2010 AAN and 2011 SCCM/AAP/CNS guidelines [12, 27, 35, 55]. Although there is no underlying physiological basis for repeating clinical examinations, this may aid to keep a low diagnostic mistake and a high familial trust for what is declared. Similarly, the length of the inter-examination observational period was not specified on a scientific basis. However, according to WBDP guidelines, a suitable time must be provided to declare BD/DNC, while the 2011 SCCM/AAP/CNS guidelines emphasize 24 h (hours), and 12 h for neonates (<30 days) and those below eighteen years, respectively. Assessment of a neonate or infant should be completed by a pediatric specialist trained in critical care. However, brain death cannot be diagnosed in preterm infants less than 37 weeks of gestational age [12, 35].

**Table 2** Spinal-mediated reflexes for cases with BD/DNC

#### Spinal-mediated reflexes in patients who exhibit clinical standards for BD/DNC

- Impulsive extensors postures
- Myoclonus
- Slow flexion and then toes Extension
- Intermittent head rotation
- Isolated thumb extension

### Diagnostic pitfalls

Some observations during the clinical evaluation of BD/DNC may be confusing to the examiner and it should not be misunderstood as an indicator of the survival function of the brainstem. While consistent with the diagnosis of

BD/DNC, these observations are not necessarily present in all cases. “*Lazarus sign*” is a pattern of the spontaneous motor response of a spinal origin and may correspond to an apnea test, or episodes of hypotension and hypoxia. It may appear in the form of impulsive limb(s) movement and respiratory-like activities. Other patterns include Perspiration, flushing, tachycardia, sudden rise in blood pressure, sporadic existence of superficial abdominal or deep tendon reflexes, and Babinski response [42].

### Apnea test

Apnea testing is based upon the functional ability of the chemoreceptors located in the medulla to provoke spontaneous respiratory acts in response to acidosis and hypercarbia. However, the exact CO<sub>2</sub> and pH levels that are presumed to initiate receptor stimulation are still unknown. Consequently, in the absence of a universal consensus, the WBDP guideline presumed a PaCO<sub>2</sub> ≥ 60 mmHg and pH < 7.3 to be considered as the target for apnea testing with a CO<sub>2</sub> rising rate in the range of 3–5 mmHg/min. However, for those with already present hypercapnia, a PaCO<sub>2</sub> ≥ 20 mm Hg above their known baseline should be the target. It is simply conducted with appropriate precautions by disconnecting mechanical ventilation after a period of adequate oxygenation for the patient. The test is considered positive when the patient shows no respiratory movement at all despite PaCO<sub>2</sub> being maintained above 60 mmHg for 8–10 min [6, 12, 35, 55].

The indications and contraindications for apnea testing are summarized in Table 3. In accordance with suggestions on the number of clinical assessments, one apnea testing in adults and two in pediatric cases are a must to declare BD/DNC according to WBDP guidelines.

However, no clear facts validate the repetition of the apnea test. It is considered a declaration of death once a comprehensive clinical examination and apnea testing has been completed provided the PaCO<sub>2</sub> threshold and pH are reached, and then, the patient fails to breathe [12, 35, 55].

### Confirmatory and ancillary testing

These tests are optional in almost all known guidelines and are reserved for the case when a clinical diagnosis is in doubt or impossible to perform properly. Confirmatory (ancillary) testing aims to evaluate the absence of intracranial and cerebral blood flow or brain electrical discharge. It is essential to realize that there is no necessity to ascertain the death of each neuron in the brain to establish brain death. For instance, even after cerebral hemispheres and brainstem death, there is still a neuroendocrine function maintained [26]. It includes EEG (electro-encephalogram) revealing absent electrographic reactivity seen after powerful stimuli, either audiovisual or somatosensory, CT (computerized tomography), evoked potentials, transcranial Doppler, magnetic resonance angiography (MRA), four-vessel catheter angiography (absent intracerebral filling observed in the carotid or vertebral vessels at the skull entry-level and preserved flow in the external carotid artery), and radionuclide cerebral perfusion scan, however, MRI (magnetic resonance imaging) is not yet undertaken as one of the ancillary tests. These tests are conducted in case of inability to accomplish a clinical examination or apnea test. Other values are to minimize the inter-examination observation period, the presence of an effect to the received medications, or to help the family to consider the BD/DNC diagnosis, serious laboratory imbalances and uncertainty about drug excretion or elimination that may potentially contribute to the failure of cerebral neurological functions (Table 4) [12, 29, 35, 55].

According to WBDP, ancillary tests are obligatory in the case of *pure* brainstem pathology if the whole-brain formulation was pursued. Of notice is that brainstem design is followed in some other regions of the world, mostly the UK (United Kingdom) as opposed to the whole-brain design of death by neurologic criteria which are promoted by WBDP. However, these tests are not 100% specific or sensitive which is a relative drawback. After accomplishment of as much of the clinical evaluation and apnea testing as can be completed, if the results

**Table 3** Indications and contraindications for apnea testing

Indications for apnea testing	Contraindications for apnea testing
-Presence of a contraindication to clinical examination	-Systolic blood pressure < 90 mmHg
-Deeply comatose patients	-Safety worries
-The absence of brainstem reflexes	-Upper Cervical spine trauma
	-Marked acidosis (pH < 7.20)
	-Hypoxemia (po <sub>2</sub> < 90 mmHg) due to COPD (chronic obstructive pulmonary disease), or cyanotic cardiac diseases
	-Marked obesity

**Table 4** Summary of prerequisites, diagnosis, and ancillary tests for brain death/death by neurologic criteria

<b>Prerequisites for BD/DNC</b>	
Evident Etiology	<ul style="list-style-type: none"> <li>-Establish that patient has a known diagnosis that has resulted in irreversible coma</li> <li>-Exclude mimicking conditions</li> <li>-Establish that brain injury is irreversible</li> <li>-Neuroimaging should demonstrate evidence of an acute central nervous system injury consistent with the profound loss of brain function</li> </ul>
Observation period before the (first) Neurologic examination	Minimum of 24 h after resuscitated cardiac arrest, rewarming after therapeutic hypothermia or birth asphyxia
Temperature, Blood pressure	≥ 36 °C, Systolic blood pressure ≥ 100 mm Hg or mean arterial pressure ≥ 60 mm Hg in adults and age-appropriate in pediatric patients
Intoxication	<ul style="list-style-type: none"> <li>-Exclude intoxication by any substance that can depress the central nervous system by drug screen, ensuring serum level does not exceed the therapeutic range, and waiting at least 5 half-lives, taking hepatic or renal dysfunction into consideration</li> <li>-Exclude pharmacologic paralysis with a peripheral nerve stimulator</li> </ul>
Laboratory tests	Exclude severe electrolyte, acid base, and endocrine disturbance
<i>Diagnostic tests</i>	
-Number of examinations	-One in adults and two in pediatric patients
-Number and Qualifications of examiners	-One Practitioner who have completed training, licensed to independently practice medicine, and trained in determination of BD/DNC, counseling families at end of life, and managing devastating brain injuries. Pediatric patients should be evaluated by experienced pediatric clinicians with specialty in neonatology, neurosurgery, pediatric critical care, pediatric neurointensive care, pediatric neurology, or trauma surgery. One in adults and two in pediatric patients
Items of clinical examination	<ul style="list-style-type: none"> <li>Exam. for unresponsiveness</li> <li>Exam. for absence of motor response of face/extremities</li> <li>Exam. for absence of pupillary light reflex</li> <li>Exam. for absence of oculoccephalic and oculovestibular reflexes</li> <li>Exam. for absence of corneal reflex</li> <li>Exam. for absence of gag and cough reflexes</li> <li>Exam. for absence of sucking and rooting reflexes(neonates)</li> </ul>
<i>Ancillary testing</i>	
Indications	<ul style="list-style-type: none"> <li>-Components of the examination cannot be completed because of the underlying medical condition</li> <li>-Uncertainty regarding interpretation of spinal-mediated motor reflexes</li> <li>-High cervical spine injury</li> <li>-Uncertainty about drug elimination</li> <li>-Severe metabolic, acid–base, or endocrine derangements that cannot be corrected and are judged to potentially be contributing to loss of brain function</li> <li>-The whole-brain death formulation is being followed and there is isolated brainstem pathology Law/ regional guidance mandates ancillary testing</li> </ul>
Recognized Tests	<ul style="list-style-type: none"> <li>-Four-vessel catheter angiography</li> <li>-Radionuclide cerebral blood flow scan</li> <li>-Transcranial Doppler (adults only)</li> <li>-EEG only if mandated by regional law or policy or if craniovascular impedance has been affected by open skull fracture, decompressive craniectomy, or an open fontanelle/ sutures, in which case it should be performed in conjunction with somatosensory and brainstem auditory evoked potentials</li> </ul>
<i>Apnea testing</i>	
Contraindications	<ul style="list-style-type: none"> <li>-High cervical spine injury</li> <li>-Chronic hypoxemia due to cyanotic heart disease</li> </ul>
Apnea testing target	-pH < 7.3 and PaCO <sub>2</sub> ≥ 60 mm Hg unless the patient has preexisting hypercapnia, in which case target should be ≥ 20 mm Hg above baseline, if known
When to abort testing	<ul style="list-style-type: none"> <li>-Spontaneous respirations witnessed</li> <li>-Systolic blood pressure &lt; 100 mm Hg or mean arterial pressure &lt; 60 mm Hg</li> <li>-Sustained oxygen desaturation &lt; 85%</li> <li>-Unstable arrhythmia</li> </ul>

**Table 4** (continued)**Prerequisites for BD/DNC**

Number and Technique	<ul style="list-style-type: none"> <li>-One in adults and two in pediatric Patients</li> <li>-Preoxygenate for at least 10 min with 100% oxygen</li> <li>-Ensure PaCO<sub>2</sub> 35–45 mm Hg</li> <li>-Preserve oxygenation with an insufflation catheter placed through the endotracheal tube (except in neonates, infants, or young children)</li> <li>-Consider use of CPAP on the ventilator or via resuscitation bag</li> </ul>
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are uniform with the BD/DNC and confirmatory testing is matching with BD/DNC, the time of death is the time that the confirmatory test findings are officially interpreted and documented [12, 27, 35, 55, 56].

**Announcement about BD/DNC**

When brain death has been established, the patient is legally and clinically declared as dead at the time of decease after testing. Then, according to the preference of the patient or family, cardiopulmonary support must be taken out, or preparations intended for organ harvest should start. Satisfactory documentation of all conditions of the diagnosis of brain death should be contained within the patient's medical records [8]. Once the clinician feels confident that the patient may encounter the BD/DNC criteria, education of the family about what is BD/DNC must begin. It should be delivered consistently and clearly with a lot of patience, empathy, and consideration for local cultural ideas. It is necessary to clarify the validity of the equivalence between BD/DNC—as legal death—and loss of cardiopulmonary functions. The need to obtain consent to conduct a BD/DNC assessment (including ancillary or apnea testing) was recently omitted by the WBDP Guidelines through a note published in 2019 by the AAN [12, 25, 43]. The objection made by some families to taking the above test or even stopping organ support after BD/DNC must sometimes be taken into account, and the reasons behind this may be moral ideas, religious beliefs, guilt or grief, distrust, and hope that the person may regain consciousness [25, 26]. Therefore, multidisciplinary teamwork must be involved in handling and management of the confronted objections. The teamwork includes palliative care specialists, hospital lawyers or administrators, and social workers [12, 35, 55].

**Brain death, ethics and organ donation**

The diagnosis of “brain death” has created a new category of definition of the dead that does not fit with society's expectations of death and its perception of the usual idea of typical death. Great stress is created for families and friends. So many of them look for a while to adapt to the unexpected heartbreak and desperation of the situation. This will aid to obtain full trust in their doctor and what

he tells about the diagnosis of brain death. Great support, caring and a successful channel of communication with the members of the family, are vital prior to ask for organ donation. Thus, after brain death has been confirmed, the only reasonable motivation for continuing treatment is organ donation. The transplant teamwork takes on additional care once written consent from the family is ready [11, 45].

Despite the apparent disparities, the clinical identification of whole-brain and brainstem death is the same, though the different roles of applied confirmatory tests. Some critical brain areas persist viably and exhibit integrated neurological functioning even after clinical diagnosis of brain (stem) death. These comprise EEG activity and hypothalamic function. Victims with maintained cortical brain electrical discharge or intracranial and cerebral blood flow are counted dead in nations that apply the brain stem formulation, but not dead in those applying whole-brain formulation. A lesser burden of proof is needed for brain stem death than whole-brain death [49].

Clinical notes point to that cardiac-beating organ donors might sporadically have remaining cerebral functions, including neuro-endocrinal reactions to nociceptive and painful stimuli throughout the harvestings' process [20]. Hemodynamic responses may be induced in donors who are subjected to surgical procurement without general anesthesia [58]. The Dead Donor Rule (DDR) [44] is the validation of the commonly supported belief that it is criminal when to kill the life of somebody to rescue another, hence concluding that individuals must already be dead before removal of vital organs, a procedure that would make them killed. The DDR is neither a regulation nor a law—it is an explanation of an ethical standard: a body part donor must be dead prior to the removal of vital organs.

The medico-legal effects of certifying brain death depend largely on the cultures and traditions dominating in different communities and its analysis on a case-by-case basis. However, it is wise to follow the *Autonomy concept*, which is the right to prevent unwanted interferences rather than a right to obtain any curative medication, but useless or cost-ineffective. This means that once an individual is brain dead, it is not ethical at all to maintain treatment [11]. Fortunately, many medicolegal

authorities have followed this approach based on the fact that stopping the futile medical efforts of those who have already died does not mean that withdrawing life support devices will allow the individual to die. Advantages are minimizing human suffering, reasonable consumption of the restricted ICU (intensive care unit) resources, and growth in the accessibility of viable organs ready for donation. Finally, medical staff must provide patients' families with data that their entire cognitive and vital functions have been permanently ceased, or else they may have false beliefs for their loved one's recovery [30].

## Controversies in brain death

### Islamic religious perspectives

Although brain death in Islam lacks consensus, death is defined as the exit of the soul from the body. Unlike other communities, the concept of brain death was included in the legal description of death in Islam in 1986 with the "Fatwa of the Islamic Fiqh Academy of the Organization of the Islamic Conference on the resuscitation device". The medical development and ethical debates in Western countries over the past twenty-five years have launched the "Islamic jurisprudence debate on brain death." However, further updates and development of Islamic bioethics are still pending to keep pace with continued progress in this regard [4, 17]. Unlike the current UK guidance, The High Committee on brain death in Saudi Arabia stipulates on carrying out a formal EEG prior to approving the diagnosis of brain death. While the rest of the ancillary tests are elective. Islamic and health care scientists equated the death of brain stem, and permitted the elimination of life support measures after a meeting of the Islamic Organization for Medical Sciences (IOMS) in 1985 [5, 9]. Later by 1986, the fatwa issued by the "Islamic Fiqh Academy of the Organization of the Islamic Conference" on resuscitation devices included the concept of brain death in the forensic description of death [2]. The death of an individual is declared legally, and accordingly, all the conditions of the law in Islam apply in the event of death if one of the following two conditions is fulfilled:

1. The presence of a complete and irreversible cessation of heart and lung functions.
2. The presence of a total and irreversible cessation of the entire brain function with the onset of disintegration.

Several Islamic countries implemented this designation of death following the endorsement of what is known in the USA as the Uniform Determination of Death Act (UDDA), which declared that: A person who has suffered either (1) permanent stop of cardiac and breathing functions, or (2) permanent stop of entire brain function,

including the brain stem, is dead. A diagnosis of death has got to be completed in agreement with the recognized medical measures. (The National Conference of Commissioners on Uniform State Laws 1981) [36].

In December 1987 and its Decree No. 2, the Council of Islamic Jurists of the Muslim World League, held in Makah Al-Mukarama, refused to equate heart death with brain death. Though it is not accepting brain death as a human loss of life, it supported previous fatwas on organ donation and transplantation. Organ procurement is allowed only if an irreversible cessation of the cardiovascular system has been documented [1]. However, although the Islamic jurisprudential debate on brain death was launched 25 years ago in response to Western ethical deliberations, further renovation and development of Islamic bioethics are still pending to keep pace with the continued progress in this regard [22, 38].

### The Egyptian perspectives and current status

While in the medical system of North America, the death of an individual is related to the stop of cerebral function (i.e., brain dead), in Egypt, any mark of biologic signs of life is an indication of the existence of the soul, even if it is fleeting. Dr. *Safwat Lutfi*, an intensivist and anesthesiology consultant from the Egyptian "Cairo University's Faculty of Medicine", started a movement to inform medical practitioners and religious leaders and scientists the dangers of recognizing 'brain death' as a medical reality. The majority of Egyptian doctors did not hold that transplantation of organs in all its kinds should be considered illegal (as Dr. *Lotfi* declared), even if a lot of them have maintained contradictory positions on the more debatable differences. Significant reactions were found among medical practitioners, in the media, religious scholars, and Parliament, in response to Dr. Lutfi's lobbying efforts regarding the uncertainty of brain death and its use to validate organ procurements, thus indicating that he deeply touched a sensitive issue in the common practice of medical services [15, 16]. Contrary to Northern American states and other Islamic countries, doctors, as well as congresspersons in Egypt, were unsuccessful in "reinventing a new death" utilizing the mass media [14]. The USA, Canada, Kuwait, Saudi Arabia, Jordan, Iran, and many other countries have approved regulations that identify brain-dead persons as dead, hence allowing organ procurements. Nonetheless, in Egypt, a national organ transplantation program persisted to be suspended from the occasion of the first successful renal transplantation surgery in 1976 to the routine release of law in April 2010, which has not yet put the procurement of organs into the current practices. Legislators, theologians, and clinicians still argue on whether brain death can ethically and legitimately be equated with a person's

death [15]. In Egypt, death does not become under technological management, nor does it become invisible as in the areas where brain death had been medically accepted. Death is indeed understood to be so imbued with religious values that no new meaning has to be given to it in order to “understand senseless suffering,” which is how living members of the American family are prone to explaining their motivation to donate their loved one’s organs [46, 47, 59]. The state of the debate about brain death in the Egyptian community also shows the failure of their government to face fruitfully the multiplicity of opinions that appeared in evaluating the condition of brain-dead patients. Nothing but one way to participate effectively in this pluralism is to draw out the numerous problems that have become associated with this discussion—from socioeconomic inequality to the logistics concerned in transferring and managing organs, the economic burden of these operations, and admiration for the dying and the dead. All such queries continued unaddressed and ignored, with a great media frenzy around the long-standing figures questioning the progress of sciences against religious and cultural conservatism. Such figures mask the appropriate diagnosis and formulation of the question. This means that asking whether a patient is brain dead is “really” dead is unlike asking whether the medical procedures can legitimately assess the profits of treating organ failure peoples against the expenses of hastening cardiopulmonary death for brain-dead patients. Because the several apprehensions precipitated by organ procurement were seen as “religious extremism”—rather than justifiable and sensible concerns about fairness and justice—the move toward an effective national organ transplant program in Egypt has been forgotten for more than three decades [3, 15, 16, 53].

## Conclusion

The accurate and objective methodology must be followed in order to issue error-free declarations of death by defining BD/DNC. Concerning the currently accepted 2011 SCCM/AAP/CNS and 2010 AAN guidelines for BD/DNC identification, practitioners must learn to be familiar with their standards as well as the contents of the WBDP standard, which announces an updated International Agreement Report on BD/DNC and certified by 5 International federations and 27 professional medical communities from all over the world.

## Abbreviations

AAN	American academy of neurology
AAP	American academy of pediatrics
ATP	Adenosine tri-phosphate
BD/DNC	Brain death/death according to neurological criteria
CNS	Child neurology society
COPD	Chronic obstructive pulmonary disease

CT	Computerized tomography
DDR	Dead donor rule
EEG	Electro-encephalogram
Hrs.	Hours
ICP	Intracranial pressure
ICU	Intensive care unit
IOMS	Islamic Organization for Medical Sciences
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
PVS	Persistent vegetative state
SCCM	Society of Critical Care Medicine
UDDA	Uniform Determination of Death Act
UK	United Kingdom
USA	United States of America
WBDP	World brain death project

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