ACTA Scientific Neurology (ISSN: 2582-1121)

Volume 7 Issue 7 July 2024

Clinical Review

Brain Death: A Comprehensive Review

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DOI: 10.31080/ASNE.2024.07.0749

Received: April 19, 2024

Published: June 06, 2024

Abstract

"Thanatology" or the science of death, has its roots planted into mankind since centuries and has amazed and perplexed scientists equally worldwide. Not late until about half a century ago, death was considered a defined point in one's life, where his/her very existence ends. However, with the exponential burgeoning of understanding of physics and biology and introduction of sophisticated life supporting equipments like "mechanical ventilators" and the easy availability of the same to the public has literally blurred that "specific time point" which defines death. With this comes another intriguing question with legal implications, is when to declare death. With increasing promotional activity from Governments for Cadaveric Organ Donation, the declaration of death is mandated and hence the onus of responsibility rests on the doctor to take the decision. With the lack of an "Unified Criteria" for defining death worldwide, the question has largely remained unanswered, even though the criteria published by American Academy of Neurology (AAN) in 1995, has largely answered the same except for pending universal acceptance worldwide. With further growth of scientific knowledge and expertise in understanding of life process, a Unified Diagnostic Criteria for brain death with universal acceptance will deload doctors of the apprehension and guilt of taking the "Very important" decision. This review article will aim to discuss the historical aspects of brain death, the diagnosis of brain death, the controversies relating to brain death and its relevance to the present day.

Keywords: Brain Death; Brain Injury

Introduction

Brain death implies a global and permanent cessation of all integrated brain functionalities including consciousness and lack of spontaneous respiratory drive, although part of these functions may be artificially maintained indefinitely with advanced life supporting measures. Hence, a diagnosis of brain death is equated to the death of the whole individual resulting from an unrelenting brain injury advancing to a state of irreversibility. Most acute injury to the brain are treatable or reversible, but brain death connotes to massive and catastrophic brain injury with irreversible coma with the absence of all brainstem reflexes.

Due to the advancements in critical care, brain death has emerged as an important issue in the past few decades as patients who are having severe, irreversible and nearly total brain dysfunction, can be maintained on a ventilator nearly indefinitely. Thus, in such situations the fundamental question arise as to whether these patients are alive or death.

Along with the clinical aspects of declaring a person as brain dead, medico-legal aspects need to be addressed since organ donation and transplantation have emerged as an important field in the medical science. Brain dead patients are good candidates for donating vital organs, so specially in the developed countries where organ donation and transplantation are on the rise, physicians or neurologists have to face medico-legal issues in regard to declaration of a person as brain dead.

What is brain death?

Brain death is defined as loss of all clinical signs of brain and brainstem function due to a major destructive lesion in a deeply comatose patient [1]. Brain death is also referred to as "death by neurologic criteria", a clinical state that involves an apneic patient with irreversible coma and absent brainstem reflexes. This has to be differentiated from other comatose states and persistent vegetative states. Brain death is based on a detailed and thorough clinical evaluation. Brain death is relatively uncommon as the brainstem is very resilient to injury. It occurs in the setting of severe traumatic brain injury, aneurysmal subarachnoid hemorrhage, massive intra-parenchymal hemorrhage or due to metabolic encephalopathy or anoxic ischemic brain injury.

Before proceeding with brain death evaluation, the irreversible cause of coma should be established and there should be no confounding factors for the neurological examination. Brain death is a result of acute and severe brain injury progressing from a hemispheric lesion to a brainstem lesion. Brainstem injury mostly advances caudally from the mesencephalon to the medulla oblongata, and usually all pontine reflexes have disappeared before the medulla oblongata stops functioning.

A brief history on brain death

During the 1950s, mechanical ventilators gained their widespread use allowing the physicians to support the physiological functioning of patients who have severe neurological injuries who lacked a respiratory drive and who would otherwise die within minutes from lack of oxygen to the brain. Physicians had ethical issues regarding the treatment of patients who are helplessly unconscious or are considered to be in a state of coma depássé (beyond coma) as withdrawal of life support were considered unethical but at the same time, continuing support to such patients give financial burden to the family members and the hospitals. Concerns regarding the emotional toll on the family members were also raised, as the family's grieving process were kept in a prolonged period of uncertainty.

During this same time, organ transplantation also started showing promising results. With the rise in demand for renal, cardiac and hepatic transplantation, proper and timely procurement of these organs became of paramount importance. As these organs are prone to ischemia, the organs removed from a body with continuing circulation- provide the greatest opportunity for a successful transplantation. Thus, the patients of irreversible coma are ideal candidates fororgan donors as their vital organs are still perfused with physiologic circulation.

To address these concerns, an Ad Hoc Committee of the Harvard Medical School published a set of guidelines in 1968 to define the condition of irreversible coma, along with clinical guidelines for its diagnosis [2], and asserted that irreversible coma should be considered "a new criterion for death". It defines brain death a state of irreversible coma substantiated by unreceptivity and unreactivity to any external and internal stimuli along with absence of any muscular or breathing movements and unelicitable brainstem reflexes for a period of 24h as confirmed by a flat electroencephalogram [2]. (Table 3).

Following this, several US states began to develop laws permitting physicians to declare patients on mechanical ventilators to be dead based on the absence of brain function. However, there were legal ambiguity since the very same patient could be dead in one state but alive in another, as not all states adopted such guidelines. In 1995, the American Academy of Neurology (AAN) published the practice parameters for the diagnosis of brain death [3]. This was adopted by other countries to define death by neurological criteria though variations occur among countries in their practice and laws. In some countries, the 'whole brain' concept of death, in which all functions of the entire brain are required for the diagnosis, is not followed. For example, the United Kingdom advocates a 'brainstem death' concept, arguing that the cessation of all brainstem functions is sufficient for death Japan, foregoing initial resistance has of lately accepted the concept of whole brain death.

Prerequisites before examination of a suspected patient of brain death

- The cause of coma should be known and there should be brain imaging findingsexplaining coma.
- Confounding factors like hypothermia, drug intoxication or poisoning, effects of sedative drugs, analgesics or neuromuscular blocking drugs, severe electrolyte disturbances, hypoxemia or hypotension have to be first corrected or excluded.
- A period of at least hours should have passed after the onset of the brain injury to excludethe possibility of recovery.

- Patient should be first treated aggressively with hyperosmolar agents, ventriculostomy orby surgical evacuation of any space occupying lesions producing brainstem displacement.
- On clinical examination, there should not be findings which are incompatible with brain death including- nystagmus or other spontaneous eye movements, conjugate eye deviation, pin point pupils, grimacing to noxious stimuli and decerebrate or decorticate motor posturing.

After all the confounders are excluded or treated and all the prerequisites are observed, the clinician can proceed for the diagnosis of brain death.

Diagnosis of brain death

A detailed clinical examination of the brainstem reflexes is the key to the diagnosis of brain death. Tests of brainstem reflexes including pupillary light reflex, corneal reflex, oculocephalic reflex, oculovestibular reflex, gag reflex and cough reflex (Table 2) and test of motor response to pain are first carried out. If all these tests are suggestive of absent brainstem reflexes, apnea test is then carried out to confirm the clinical diagnosis of brain death. Occasionally, other electrophysiological or radiological investigations may be employed. These tests are to support the clinical diagnosis of brain death by demonstrating the absence of blood flow to the brain or absence of electrical activity of the cortex. However, these tests should not replace the clinical assessment as they are inaccurate and results of the test may not be consistent. These ancillary tests are best avoided, but they are mostly used in the setting where there is inability to perform an apnoea test due to chronic hypoxemia, hemodynamic instability or chronic CO_2 retention.

Region of brainstem	Function	Effect of lesion
Core of brainstem (reticular formation-reticular activating system)	Consciousness	Coma
Respiratory centers in pons and medulla	Respiratory drive	Apnea, loss of spontaneous Breathing
Cardiac and vasomotor centers in medulla	Maintains BP, heart rate	Fluctuating BP, heart rate
All motor and sensory pathways (except vision and smell)	Mediates motor and sensory impulses	Bilateral paralysis, complete Anesthesia
Cranial nerve nuclei	Mediates cranial nerve functions and reflexes	Bilateral loss of cranial nerve functions and reflexes

Table 1: Parts of brainstem with associated functions and effects of lesion (Adopted and Modified from Dhanwate AD. Brainstem death: A comprehensive review in Indian perspective". *Indian Journal of Critical Care Medicine* 18 (2014): 596-605).

Reflex/test	Test for	Cranial nerve nuclei/ center located in
Pupillary light reflex	Cr. N. II, III	Midbrain
Vestibulo-ocular reflex/caloric test	Cr. N. III, VI, VIII	Midbrain, pons
Oculocephalic reflex (doll's eyes phenomenon)	Cr. N. III, VI, VIII	Midbrain, pons
Corneal reflex	Cr. N. V, VII	Pons
Pharyngeal (gag) reflex	Cr. N. IX, X	Medulla
Cough (tracheal) reflex	Cr. N. X	Medulla

Vagus nerve function (atropine challenge)	Cr. N. X	Medulla
Response to painful stimulation in trigeminal nerve distribution	Cr. N. V, VII	Pons
Apnea test	Respiratory centers	Pons and medulla

Table 2: Tests for brainstem functions (Adopted and Modified from Dhanwate AD. Brainstem death: A comprehensive review in Indian perspective". *Indian Journal of Critical Care Medicine* 18 (2014): 596-605.

Unresponsive coma
Apnea
Absence of brainstem reflexes
Absence of spinal reflexes
Isoelectric electroencephalogram
Persistence of conditions for at least 24 hours
Exclusion of drug intoxication or hypothermia

Table 3: Harvard Criteria for Brain Death (1968).

From Ad Hoc Committee of the Harvard Medical School [2].

Clinical tests for diagnosis

Tests of brainstem reflexes

Pupillary response to light

A widely dilated or mid position pupils may be seen, most pupils in brain death have a 4- to 6-mm diameter with absence of pupillary response to bright light. On testing of light reflex the pupils have to be observed closely at least for one minute to allow time for any slow response to occur. A magnifying glass or a handheld pupillometer can be helpful if there is a doubt regarding the pupillary response. Presence of a widely dilated pupil is not required but absence of light reflex is mandatory. Constricted pupils should not be seen and should raise the concern of medication effect.

Corneal reflex

Corneal reflexes should be absent bilaterally, tested by squirting water on the cornea or by touching it with a tissue or a wisp of cotton, and no blink response should be seen with any stimulus.

Repeated stimulations should be avoided as it may cause corneal abrasions.

Oculocephalic reflex

Oculocephalic reflexes also called as doll's eye phenomenon is tested by sudden fast turning of the head to one side produce eye movements to the contralateral side denoting the integrity of the medial longitudinal fasciculus in the brainstem. This reflex should not produce any ocular movement in brain death.

Oculovestibular reflex

To elicit an oculovestibular reflex, patient's head is placed in the center and lifted to 30 degree from supine position. A soft catheter is introduced into the external auditory canal and a slow irrigation with at least 5 ml of ice-cold water is performed while the eyes are held open by an assistant. The eyes are observed for one minute after the irrigation is completed before repeating the test on the other side. An intact oculovestibular reflex causes tonic deviation of the eyes opposite to that of the irrigated ear. This reflex is absent in a brain dead patient, and any movement of one or both eyes, whether conjugate or not, excludes the diagnosis of brain death.

Gag reflex

Gag reflex is absent in a patient who is brain dead. This test may be difficult to perform in intubated patients, in such cases, testing of gag reflex may be carried out by passive movement of the endotracheal tube or sticking a finger deep in the mouth to move the uvula or stimulating the palate or pharynx by using a tongue depressor.

Cough reflex

The cough reflex should be tested by deep bronchial suctioning with an endotracheal suction catheter and with at least two passes. The patient is closely observed for any cough response or movements of the chest or diaphragm. Cough reflex should be absent in brain dead patients.

Test of motor response to pain

On applying standard noxious stimuli including compression of the supraorbital notch, deep pressure on the fingernail bed or compression on the temporo-mandibular joint or sternal rubbing should produce no motor response. Some reflex motor responses may be preserved, and the challenge is to identify them as spinal reflex responses.

Spinal reflexes may occur with neck flexion and nail bed compression but are not seen with supraorbital nerve compression. These responses are uncommon and include reproducible triple flexion responses, finger flexion or extension, head turning, and slow arm lifting. These movements appear to be more common in children and young adults. These movements cause concern for the family members and must be properly explained and documented in the medical record.

When all these brainstem reflexes are absent and no breathing effort is apparent, the physician can proceed with the next step: the apnea test. In apnea test, the absence of a breathing drive is proven with a carbon dioxide challenge.

Apnoea test

Patient is prepared by pre-oxygenation with 100% FIO_2, reducing positive end-expiratory pressure [PEEP] to 5 cm of water and drawing a baseline blood gas. Mechanical ventilation is then disconnected while 100% oxygen is delivered at 6L/min by oxygen flow catheter placed at the level of the carina.

The contraindications for apnoea test are- hypotension (SBP <90mmHg), hypoxaemia (SPO2 <90%) and severe acidosis (pH <7.2).

The components of the apnoea test include absence of spontaneous respiratory efforts during a period of disconnection from the mechanical ventilator, with the arterial pCO2 reaching a critical point (taken as ≥60 mm Hg) without the presence of hypoxaemia during this period. Any respiratory movement should be closely observed during this period. If there is a doubt regarding the presence of any respiratory movement, a spirometer can be connected to confirm the absence of any tidal volume.

The arterial blood is drawn again at 10 minutes, after which the ventilator is reconnected.

The blood drawn is tested again for arterial pO2, pCO2, and pH. If respiratory movements are absent during the time of disconnection of the mechanical ventilator and the arterial pCO2 is ≥60 mmHg or there is a 20mmHg increase in the pCO2 over the baseline value, the apnea test is positive. Positive apnoea test is diagnostic of brain death.

If respiratory movements are observed, apnoea test is negative. If during the apnoea test, the SBP drops to <90 mmHg or there is a drop in the SPO2 to <90% in the pulse oximetry or cardiac arrhythmia occurs, the test has to be stopped, arterial blood gas sample should be drawn immediately and the ventilator has to be reconnected. If the arterial blood gas analysis at this point showed increase in the pCO2 ≥60 mmHg, the apnoea test is considered positive, but if the arterial pCO2 is <60 mmHg the result is indeterminate and has to be repeated later.

core body temperature ≥ 36.5 ºC
SBP(Systolic Blood Pressure) ≥ 90 mm Hg
Euvolemia (option: preferably positive fluid balance in the previous 6 hours)
Normal PCO2. Option: arterial PCO2 >40mmHg
Normal PO2. Option: preoxygenation to obtain arterial PO2 >200mmHg

Table 4: Pre-requirements for Apnea Test [17].

Ancillary tests

EEG

A minimum of 8 electrodes with inter-electrode distance at least 10cm should show electrocerebral silence [6-8].

Electrocerebral silence is defined as no electrical potential greater than 2mV during a 30-minute recording time.

EEG can show artifacts from the ventilator or the surrounding electrical devices, patient of profound hypothermia or drug overdose may have flat EEG. Despite these disadvantages, EEG continues to be the most widely used supplementary test for the diagnosis of brain death. EEG remains strongly recommended in the United States and is an essential part of the American criteria for the diagnosis of brain death in very young children [9].

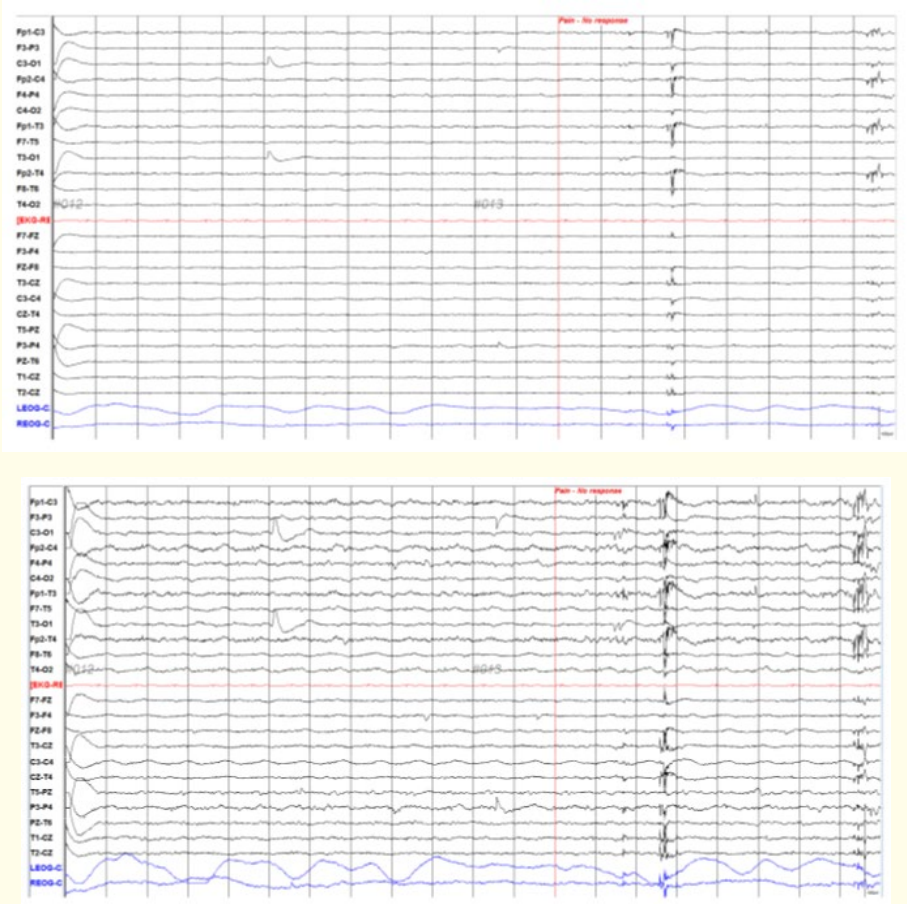

Figure 1: EEG of a 70-year-old comatose male recorded 3 days after cardiopulmonary arrest. (A) The EEG appeared flat at sensitivity 7 μV/mm without any reactivity to painful stimuli. (B) Low-voltage, mixed-frequency activity was seen at sensitivity 2 μV/mm in the same epoch, which could not be eliminated. The patient never regained consciousness, spontaneous respiration, or brainstem reflexes after the cardiopulmonary arrest. A repeat EEG performed 12 days after the arrest showed the same pattern. EEG, electroencephalography [18].

Sensory evoked potentials

Tests for somatosensory and brain stem auditory evoked potentials show no response in brain death [10]. But these tests have limited utility as the functional integrity of only a specific pathways are tested. However unlike EEG, these tests are minimally affected by sedative drugs and anaesthetics.

Angiography

In conventional angiographic studies, there is absent blood flow at or beyond the carotid bifurcation or circle of Willis in case of brain death [11]. The disadvantage of the test is the invasiveness of the procedure. Recently, clinicians have used MR or CT angiograms in lieu of the more invasive traditional angiography.

Transcranial doppler ultrasound

The transcranial doppler is a safe and non-invasive test that can be performed at the bedside. Both the anterior and posterior circulation has to be evaluated [12]. The test requires expertise. The Assessment Subcommittee of the American Academy of Neurology has accepted transcranial Doppler ultrasonography as a reliable procedure for confirmation of brain death [13]. However, in 10-25% of patients, temporal bone thickening precludes the

evaluation of some of the insonated intracranial arteries, in such cases, the initial absence of Doppler signals cannot be interpreted as a finding consistent with brain death. Transcranial Doppler (TCD) was found to be highly sensitive in determining absent cerebral perfusion.

Pitfalls in diagnosis of brain death

There can be misinterpretation of the ancillary tests if they are solely used as a diagnosticmodality, examination of a patient with confounding factors (drug intoxication, hypothermia, shock etc) may lead to in errors in the diagnosis of brain death.

Controversies regarding brain death

Persistent controversies remain regarding the diagnosis of brain death, as to whether the clinical tests should be repeated on a later date before labelling a person as brain dead, whether ancillary tests like EEG or imaging studies should be used to diagnose brain death. Patients who meets the diagnosis of brain death can sometimes have preserved neurological functioning, like an intact hypothalamus function to maintain the regulation of free water in the bloodstream [14]. Further, some patients who satisfy the accepted diagnosis of brain death criteria may maintain an organised electrical activity on EEG [15] thus casting a doubt on the utility of ancillary tests for the diagnosis of brain death. In regard to the apnoea test, hypercarbia (which is deliberately induced in the apnea test) is known to increase ICP and therefore can worsen ischemic injury to the brain, potentially contributing to herniation, and thus can be dangerous to a recently injured brain. So, as Joffe., *et al.* wrote, "it is reasonable to suggest that the apnea test itself can result in failing the apnea test, creating a self-fulfilling prophecy." [16-19].

Ethical issues related to brain death

Families may fail to accept brain death as death, ethical problems associated with declaration of brain death mostly concern family opposition to brain death and refusal to let go. In such circumstance, the physician could continue the life support while trying to resolve this issue, However cardiopulmonary resuscitation is not warranted even under such situations.

Conclusion

To conclude, the declaration of brain death must always be recorded in the medical notes with the date and time. The legal time of death is taken as the time at which the apnea test was completed or the time that the confirmatory test was officially reported. India follows the UK practice and considers death as equivalent to brainstem death. So, medically and legally, the patient is dead, if brainstem death (brain death is used as a synonym for the latter) has been certified. The doctors involved in the diagnosis should in no way be connected with the transplant surgeries concerning the 'brainstem dead' cadavers.

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