

Brain Death and Organ Donation

Suchita Kosare¹, Apeksha Gala²

ABSTRACT

The number of organ transplantation has risen exponentially in the last few decades. The concept of brain death and the ability to harvest vital organs in a limited time have contributed to the recent success. In this review, we attempt to delineate the criteria for brain death as well as the testing methodology. The challenges and the legal aspects related to organ donation have also been discussed.

Keywords: Apnea test, Brain death, Green corridor, Transplantation of Human Organs Act.

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DEFINITION

The definition of brain death states that there is complete cessation of cerebral function wherein the proximate cause is known and is considered irreversible. The American Association of Neurology (AAN) has defined brain death with three cardinal signs: cessation of the functions of the brain including the brainstem, coma or unresponsiveness, and apnea.¹

In India, the Transplantation of Human Organs Bill was introduced in the Lok Sabha on 20 August, 1992, and became the Transplantation of Human Organ Act in 1994.²

Evaluation team: In India, according to the transplantation of Human Organs (THO) Act, 1994 (subsection 6 of section 3),³ "brainstem death" is referred to the stage at which all functions of the brainstem have permanently and irreversibly ceased. This requires certification by a "Board of Medical Experts" consisting of (1) the medical superintendent (MS)/in-charge of the hospital in which "brainstem" death has occurred, (2) a specialist, (3) a neurologist or a neurosurgeon nominated by the MS, from a panel approved by the appropriate authority, and (4) the doctor under whose care the "brainstem" death has occurred. Amendments in the THO Act 2011 have allowed selection of a surgeon/physician and an anesthetist, if an approved neurosurgeon or neurologist is unavailable.

In many countries, including India, the diagnosis of brain death is made after fulfilling the mandatory criteria and by the apnea testing which is a safe technique for documentation.⁴

A checklist of requirements⁵ that need to be fulfilled before proceeding with tests for brain death is indicated in Table 1.

For certifying brain death, the following needs to be evaluated: Presence of irreversible coma, the cessation of spontaneous respiration confirmed with apnea tests, absence of pupillary light reflexes, corneal reflexes, doll's eye movements, gag reflex, cough reflex (tracheal), eye movements on caloric testing bilaterally, motor response in any cranial nerve distribution, and motor response on stimulation of face/limb/trunk.

CRITERIA FOR ESTABLISHING BRAIN DEATH IN INFANTS AND CHILDREN

A longer time between assessments, greater than 6 hours, has been advocated in children taking in view their resilience compared to adults.⁶ This varies according to the patient's age: Term to 2-month-old: 48 hours, >2 months to 1 year: 24 hours,

^{1,2}Department of Anesthesia, HinduHrudaySamrat Balasaheb Thackarey Medical College and Dr RN Cooper Municipal Hospital, Mumbai, Maharashtra, India

Corresponding Author: Apeksha Gala, Department of Anesthesia, HinduHrudaySamrat Balasaheb Thackarey Medical College and Dr RN Cooper Municipal Hospital, Mumbai, Maharashtra, India, Phone: +91 9820146886, e-mail: appi.apeksha@gmail.com

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>1 year to <18 years: 12 hours, >18 years: as in adults. The diagnosis of brain death cannot be made in preterm infants of gestational age of less than 37 weeks. Hypotension, hypothermia, and metabolic disturbances should be treated and corrected prior to any evaluation. Pediatric specialists with critical care training should assess the neonates and infants. If there is presence of arterial PaCO₂ ≥20 mm Hg above the baseline, and ≥60 mm Hg with no respiratory effort, during the testing period, apnea testing is positive. Ancillary studies are deployed only when components of the examination or apnea testing cannot be completed safely, or there is uncertainty about the results.

Table 1: Checklist prior to proceeding with tests for brain death

Prerequisite	Details
Proximate cause for unresponsive state that is incompatible with survival	Major trauma, intracranial bleed with midline shift
Neurological imaging to confirm diagnosis	CT brain, MRI, and angiography
Exclusion of associated medical conditions that could account for unresponsiveness	Exclusion of severe acid–base, metabolic, or electrolytes abnormalities
Exclusion of drugs causing unresponsiveness	Sedatives, narcotics, and muscle relaxants. In drug overdosage, allow time for 5 half-lives/measure drug levels
Normal temperature	Core temperature >32°C/90°F

Clinical Testing of Brain Death

- Coma: Absence of response to noxious stimulus (supraorbital pressure or pressure on the nail bed) with the exception of spinally mediated reflexes.
- Absent brainstem reflexes (a formal evaluation of the brainstem reflexes is undertaken when the patient has had fixed dilated pupils and absent cranial nerve reflexes for more than 4 hours).⁷
- Apnea test: The main aim of this test is to check for the integrity of the brainstem respiratory center at high levels of blood carbon dioxide. Prerequisites include a patient who is normothermic (core temperature $\geq 36.5^{\circ}\text{C}$), hemodynamically stable (systolic pressure ≥ 100 mm Hg), free from sedative and paralytic drugs, with normal oxygenation ($\text{PaO}_2 \geq 200$ mm Hg after 100% oxygenation), and near normal PaCO_2 (35–45 mm Hg).

Oxygen is insufflated through a catheter placed at the level of the carina at 6.0 L/minute after disconnection from the ventilator. The observer looks for respiratory movements at 8–10 minute after disconnection. Assuming a rate of rise in PaCO_2 of 3 mm Hg/minute,⁸ this will result in an increase of 24 mm Hg above baseline in 8–10 minute. The test is considered positive if there are no respiratory movements at a PaCO_2 of 60 mm Hg or 20 mm Hg above baseline in those with an elevated PaCO_2 .^{5,7} Certification of brain death is after a second apnea testing, the timing of which varies between countries. In India, the apnea test needs to be repeated after an interval of 6 hours and certified by four physicians from a recommended panel; one of whom has to be a neurologist. The time of death is the time PaCO_2 reaches the target value during the second apnea test.

The increase in intracranial pressure (ICP) that accompanies brain death spares the rostral portion beyond the second cervical spine and does not compromise blood supply to this area. This could be the explanation for complex motor movements at the spinal cord level even after diagnosing brain death.^{1,7,9}

Troubleshooting during Performance of Apnea Test

- Patient's systolic blood pressure (SBP) ≤ 100 mm Hg: Vasopressors, inotropes, and fluid boluses need to be administered to keep the blood pressure (BP) above the target. The apnea test is aborted if systolic BP is ≤ 90 mm Hg and the test needs to be repeated after stabilization.
- Oxygen saturation not maintained during apnea testing: The apnea testing is terminated if the saturation is $\leq 85\%$ for more than 30 seconds.¹ The test can be retried with T-piece and a continuous positive airway pressure of 10 cm H_2O and an oxygen flow of 12.0 L/minute. Reducing the positive end-expiratory pressure (PEEP) to 5 cm H_2O prior to disconnection from the ventilator for apnea testing can predict the tolerance to apnea.
- Patient is hypothermic ($< 36.5^{\circ}\text{F}$): Guidelines for apnea testing are not valid and need to be repeated after correction of hypothermia.
- Patient repeatedly desaturates or becomes hypotensive during apnea testing: One should consider ancillary tests for confirming brain death (electroencephalography, cerebral angiography, transcranial Doppler, and scintigraphy). In India, the laws are not clear about the use of ancillary tests.
- Baseline $\text{PaCO}_2 \geq 40$ mm Hg or ≤ 35 mm Hg: A rise of ≥ 20 mm Hg above baseline can be considered a positive apnea test in patients with elevated baseline PaCO_2 . Reducing the frequency of ventilation to allow a PaCO_2 in the recommended range should be considered prior to testing for apnea.

Motor Response to Pain

There should be no motor response in the distribution of any cranial nerve. Such a response would be grimacing (facial nerve motor response) in response to thumb pressure over the supraorbital groove (trigeminal nerve sensation). Similarly, there should be no response to painful stimuli of the trunk suggesting absence of sensory nerve conduction across the foramen magnum. Neuromuscular blocking agents can produce prolonged weakness.¹⁰ If neuromuscular blocking agents have recently been administered, examination with a bedside peripheral nerve stimulator is needed.¹¹

Pupillary Response to Light

The response to bright light should be absent in both the eyes. The pupil should be observed closely for one minute to allow time for a slow response to become evident. Both widely dilated as well as midpositioned fixed pupils are seen in brain dead patients. The presence of widely dilated pupils is not a necessary criterion for brain death but fixed pupils with no response to light is a mandatory requirement for its diagnosis. The size may vary from 4 to 9 mm. Dilated pupils are compatible with brain death because intact sympathetic cervical pathways connected with the radially arranged fibers of the dilator muscle may remain intact.^{12,13}

Corneal Reflex

This should be absent. Repeated corneal stimulation is unnecessary and should be avoided. Corneal abrasions are undesirable if the patient is a potential corneal donor.

Oculocephalic Reflex (Doll's Eye Phenomenon)

This test must not be performed in patients with an unstable cervical spine. The head is turned from the starting position to a new steady position and then briskly turned toward the opposite side. The eyes move to the contralateral side denoting the integrity of the medial longitudinal fasciculus in the brainstem.

Oculovestibular Reflex

Ocular movements are absent after head-turning and caloric testing with ice water. Before testing, both the ears must be inspected with an auroscope to confirm that the tympanic membranes are intact and that the external auditory canal is not obstructed. If the eardrum is perforated, the test can be performed using cold air as the stimulus. A fracture of the base of skull resulting in blood, cerebrospinal fluid, or brain tissue in the external auditory canal is a contraindication to performing this test on that ear. The patient's head is placed in the center and lifted 30° from the supine position. A soft catheter is introduced into the external auditory canal and slow irrigation with at least 5 mL of ice-cold water is performed while the eyes are held open by an assistant. The eyes should be 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. Any movement of one or both eyes, whether conjugate or not, excludes the diagnosis of brain death. In a brain-dead patient, the eyes remain fixed. A combined ice-cold water caloric stimulation and head rotation testing has been suggested as the most profound stimulation for deeply unconscious patients.

Gag Reflex

This should be absent. A tongue depressor is used to stimulate each side of the oropharynx and the patient observed for any pharyngeal

or palatal movement. Evaluation of the gag reflex may be difficult in an intubated patient and should not be performed if extubation is required to conduct the test.

Cough Reflex

A suction catheter is introduced into the endotracheal or tracheostomy tube to deliberately stimulate the carina. The patient is closely observed for any cough response or movements of the chest or diaphragm.

Other Confirmatory Tests

Electroencephalogram, sensory evoked potential, conventional angiography, and transcranial Doppler ultrasonography.

ORGAN DONATION

“World Organ Donation Day” is celebrated on August 13 and it is dedicated to inspire people to pledge to donate their organs. Live Donor and Deceased Donor families should be recognized, acknowledged and honored in social and government events for their invaluable contribution to mankind.

Global shortage of organ donation is known fact and India lags far behind compared to other countries in the World. In India, every year 1.8 lakh patients are detected with renal failure but we perform around 6000 renal transplant per year. In India, we do approximately 10–15 heart transplants each year, when almost 5000 patients suffer from heart failure. Similarly, about 25,000 persons suffer from liver failure, and liver transplant performance rate is 1500 per year. Every year in India, 100,000 people are in need of corneal transplant, but in reality, we are able to do only about 25,000 corneal transplants.¹⁴

In India, as only few states are very active in organ donation and transplant program, there is discrepancy in demand and supply ratio.

Universally, organ donation is voluntary.

Two voluntary systems are as follows:

- Opt in—Donor him-/herself gives consent for organ donation.
- Opt out—In this system, anyone who has not refused for organ donation is considered as a Donor.

In India, we have the Opt-in system, while many western countries practice the Opt-out system.

Contraindication of Organ Donation

- IV drug/substance abuse.
- Untreated bacterial, fungal, or viral infection (treated infection may be considered).
- Malignancies other than primary brain tumors and nonmelanoma skin cancers.
- Hepatitis B or Hepatitis C donors may be acceptable for HBV/C recipients,

Consent for Organ Donation

- Person willing enrolled as Organ Donor. ICU physicians and transplant coordinator should retrieve proof of such authorization.
- A signed donor card.
- At the time of organ retrieval, consent from one of the close relatives like spouse, father, mother, daughter, son, brother, or sister is required.

- The wish to donate organs is shared with the relatives and friends.
- From 8 (for declaration cum consent): There are reasons to believe that no near relative of the said deceased person has objection to any of his/her organs/tissue being used for therapeutic purposes.

Hospital organ donation registry (HODR) coordinates the process of cadaver organ donation. During lifetime, a person can pledge for organ donation by filling up a donor form in the presence of two witnesses, one of who shall be a near relative and send the same to HODR. The organ donor form could be obtained from HODR either personally or through mail.

Organ Donation Process

- Identification of potential donor by the ICU physicians.
- Screening of donor (no active infection, malignancy, and donor age).
- Organizing for the brainstem death tests.
- Declaration of death to the relatives by the treating physician.
- Informing the ZTCC.

Challenges of Organ Donation

- High gap in demand-supply ratio.
- Inadequate infrastructure and regulation polices of government and nongovernment hospitals.
- Lack of awareness of concept of brainstem death.
- Poor rate of brainstem death certification by hospitals.
- Low deceased organ donation rate. The approach like discussion about organ donation as part of end-of-life care and an early involvement of transplant coordinators and counselors will help.
- Lack of organized systems for organ procurement from deceased donor.
- Maintenance of standards in transplantation, retrieval, and tissue banking.
- Prevention and control of organ trading.
- Cultural and religious aspects.
- Early release of deceased body to relatives for its disposal/ funeral.
- Organ donation and transplant to be a part of undergraduate study syllabus for early sensitization.
- Media support to increase the awareness among the general population.
- Organ donation awareness by celebrities.

Legal Aspect of Organ Donation

In India, brainstem death was legalized in 1994 when The Transplantation of Human Organs Act (THOA) was passed and it states “Brainstem death” as the stage at which all functions of the brainstem have permanently and irreversibly ceased and is so certified by a “Board of Medical Experts.” Almost 37 different organs and tissues can be donated after brainstem death. It includes organs, such as, kidneys, heart, liver, cornea, skin, pancreas, bones, intestine, and veins, etc.¹⁵

Transplantation of Human Organs Act (THOA), 1994, was enacted to provide a system of removal, storage, and transplantation of human organs for therapeutic purposes and for the prevention of commercial dealings in human organs. In India, THOA is adopted by all states except Andhra and Jammu and Kashmir, who have their

own similar laws. THOA has total 26 sections and each section deals with different aspects involved in organ donation.^{16,17}

Transplantation of Human Organs Act (THOA), 1994, was issued by Government of India and has been evolved with the time. THOA 1994 was further revised in 1995, 2008, 2011, and lastly in 2014.

Transplantation of Human Organs and Tissues (amendments) Act (THOTA), 2011, was approved by the Parliament and had the assent of the then President of India. Some of the important amendments under the THOTA Act, 2011, are as follows:

- Tissues have been included along with the organs.
- "Near relative" definition has been expanded to include grandchildren and grandparents.
- Provision of "Retrieval Centers" and their registration for retrieval of organs from deceased donors. Tissue banks shall also be registered.
- Provision of swap donation included.
- Provision of mandatory inquiry from the attendants of potential donors admitted in ICU and informing them about the option to donate—if they consent to donate, inform retrieval center.
- Provision of mandatory 'Transplant Coordinator' in all hospitals registered under the act.
- Provision of higher penalties for trading in organs and to protect vulnerable and poor.
- Expansion of team of brain death declaration: Inclusion of physician, anesthesiologists, surgeon, and intensivist in brain death declaration team. The brain death declaration team members should not be a member of the transplant team by law.
- National human organs and tissues removal and storage network and national registry for transplant are to be established.
- Provision of advisory committee to aid and advise appropriate authority.
- Enucleation of corneas has been permitted by a trained technician.
- Act has made provision of greater caution in case of minors and foreign nationals and prohibition of organ donation from mentally challenged persons.

After 3 years, again amendments/new rules were made in 2014, THOTA Rules. In these rules, there are further definition of certain terminologies and introduction of 21 forms, which are mandatory for live/deceased donor submission to authorization committee.

THOTA Rules, 2014, Defined Functions of Regulatory Bodies¹⁶

Functions of Appropriate Authority

- Grant, renew, suspend, or cancel the registration of hospitals and to enforce standards that have been prescribed for hospitals undertaking transplantation activities and tissue banks, which test, store, or distribute tissues.
- Investigate any complaint of breach of any of the provisions of the act and take appropriate action
- Inspect tissue banks and hospitals periodically to ensure compliance.

Functions of Advisory Committee

- To assist appropriate authority in the discharge of its functions.
- Constituted for a period of 2 years.
- A representative from NGO working in the field of organ or tissue donation.

Eligibility criteria of a transplant coordinator were defined in THOTA Rules, 2014, (rule 29). A transplant coordinator shall be an employee of the registered hospital having qualification of degree in recognized field of medicine/nurse/bachelor's/master's degree in social work, psychiatry, sociology, social science, and public health.

In brain death declaration, duty of registered medical practitioner has been defined, who with the help of transplant coordinator is expected to do the needful.

For brain death certification, appropriate authority may appoint a panel of experts in accordance with the act.

Form 7 is for pledging the organs before death.

Form 8 is for declaration by the near relative or either of the parents (in case of minors).

Form 9 applies for consent in case of unclaimed bodies.

Form 10 is for brain death certification.

Brainstem death certificate format for the first and second examinations, supposed to be done 6 hours apart, has been defined in THOTA, 2014.

Brainstem death certification would be made by registered medical practitioner (RMP) in-charge of the hospital, RMP nominated by appropriate authority, neurologist/neurosurgeon of the hospital (anesthetist/physician/surgeon in case neurologist/neurosurgeon is not available), and RMP in-charge of the treatment.

The concerned authorities/consent to be obtained in case of organ retrieval from deceased donor is as follows:

Consent of Family

For willful organ donor or family of deceased willing for organ donation, brainstem death certification is required and then it is informed to human organ retrieval center.

Unclaimed Bodies

If bodies are not claimed by a near relative within 48 hours of the death of the deceased person, the person in-charge of the management or control of the hospital or prison can authorize the removal of any organ.

Postmortem Cases

When a postmortem is required after the death of a person, the RMP will ascertain the consent of the donor/family and then make a request to the station house officer. Superintendent of police or deputy inspector general of the area will facilitate the timely retrieval of organs or tissues from the donor.

Directorate General of Health Services, Government of India is implementing National Organ and Tissue Transplant Program for carrying out the activities as per amendment act (THOTA), training of manpower, and promotion organ donation from deceased persons.¹⁸

Zonal Transplant Coordination Center (ZTCC) was formed as a coordinating agency for Mumbai and suburbs in 2001, as per the Maharashtra State Guidelines issued for cadaver transplant in 1999. It is registered under the charity commissioner's office. Human organ transplantation act was passed in 1994 in India and it was adopted by Maharashtra in 1995.

The ZTCC maintains the computerized waiting list blood groupwise for each organ like kidney, liver, heart, and lung as per the priority criteria given in the Maharashtra state guidelines. The patient's name is registered through hospital and the patients cannot get registered directly to the ZTCC. ZTCC maintains the computerized waiting list of recipients for each organ. To connect

to every registered waiting recipient with fair distribution of organs as per waiting list.

Green Corridors¹⁹

- There have been many instances where valuable organs have been wasted due to delay in the transportation process.
- A green corridor refers to a route that is demarcated and cleared out for an ambulance carrying harvested organs. The objective is to ensure that the in-transit organ arrives at its destination in the shortest time possible.
- In India, mostly road transport is being used for shipment of organs. When the distance is more, the organs are transported through commercial airlines.
- Green corridors have been particularly helpful in reducing cold ischemia time and improving the quality of organ transplant.

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