Diagnosis of Brain Death in adults; Guidelines

R Dwyer, C Motherway, D Phelan
Intensive Care Society of Ireland (ICSI)

Intensive Care Society of Ireland

PRINTROOM 04102016

Diagnosis of Brain Death in adults; Guidelines

R Dwyer, C Motherway, D Phelan
Intensive Care Society of Ireland (ICSI)

These Guidelines are based on our interpretation of the existing legal situation and 'custom and practice' in Ireland, on previously published Guidelines in Ireland and internationally, and on published literature in this area.

Introduction

Brain death as a concept is ubiquitous in medical, nursing and lay literature. There is recognition that some brain injured patients maintained on artificial ventilation develop complete and irreversible loss of brain function. Brain death is now accepted as the equivalent of cardiac death (the usual statutory cause of death). Cardiac death usually follows within days or weeks even with continuation of mechanical ventilation and full supportive therapy (1).

The ability to certify death when there is irreversible cessation of brainstem function enables specialists working in Intensive Care to withdraw futile treatment (e.g. mechanical ventilation), on humanitarian, ethical and (coincidentally) utilitarian grounds.

There is no statutory law on this area in the Republic of Ireland but draft proposals for a Human Tissue Bill in 2009 stated that "A determination of death must be made in accordance with accepted medical standards". Pending enactment of legislation, compliance with the recommendations of these ICSI Guidelines, the 2010 ICSI Guidelines (2) and the 1988 Irish Memorandum on Brain Death (3) (which are all in accordance with each other), has the legal status of 'custom and practice' in the Republic of Ireland.

History of the establishment of the criteria for brain death:

1959: Moularet P, Goudon M. Coma depassé et necrosis nerveuses centrales massives. Revue Neurologique 101 :116-139.
This was the reference publication proposing a name ('Coma depassé') for the 'death of the nervous system', the clinical, electrophysiologic and angiographic features of which had been described in the French and Scandanavian literature between 1956-1959.

1968: The concept of brain death as death was proposed by an Ad Hoc Committee of Harvard Medical School

1976: UK Royal Medical Colleges defined brain death as complete irreversible loss of brainstem function and specified clinical criteria to certify brain death.

1981: USA Presidents Commission published Guidelines. Recommended confirmatory tests to reduce the required period of observation. Recommended a period of 24 hours observation for patients with anoxic brain damage.

1988: Irish Medical Journal published a Memorandum on Brain Death from an ad-hoc Irish Working Party essentially constituting guidelines for Ireland on the clinical criteria for diagnosis of brain death (3).

1995: Australian publication of Guidelines on clinical confirmation of brain death (4).

2006: Canadian Council for Donation and Transplantation published National Guidelines for determination of brain death (5).

There are conceptual differences between the United Kingdom (which specifies brain-stem death as the criterion for determining death) and the United States, Australia and other countries which require 'death of the whole brain'. In practice the clinical tests to ascertain death are the same with both concepts and the principle of "Death by neurological criteria" has emerged, which encompasses both concepts.
There is a widespread consensus among English speaking countries on the concept and diagnostic criteria for Brain Death (5-10). These Irish Guidelines are aligned with international practice.

Approach to the Clinical Diagnosis of Brain Death:
Assessment of brain death in a comatose patient should proceed with certain principles in mind; establishing the cause of coma, ascertaining irreversibility, excluding major confounders and accurately testing all possible brainstem reflexes.

A diagnosis of brain death based on clinical tests should not be made unless the pre-conditions in A) and B) have been met.

(A) Proof that the condition of the patient is due to irreversible structural brain damage

The diagnosis of a disorder that can lead to brain death must be clearly established. A number of conditions which can cause the loss of brainstem reflexes are reversible e.g. Guillaun Barré syndrome, brainstem encephalitis, poisoning etc. If there is any doubt about the primary diagnosis, do not diagnose brain death clinically.
In each patient therefore, the underlying neurological diagnosis which caused the severe neurological injury and the accompanying loss of brain stem reflexes must be apparent and must be well documented.
Supplementary proof of sufficient brain pathology from CT scan, angiography or MRI scan is usual. Conversely, a normal CT scan can be seen early on after a cardiac or respiratory arrest. In patients with acute hypoxic-ischaemic brain injury clinical evaluation should be delayed for at least 24 hours after the cardio-respiratory arrest. However a CT scan with abnormalities consistent with brain death does not obviate the need to search for confounders.

(B) Exclusion of reversible causes of coma

a) Toxins, poisons, sedative drugs and many other agents may cause coma when patients receive large quantities. The drug history should be reviewed and if necessary a toxicology screen obtained.

b) If sedative drugs have been used, adequate time must be allowed for residual effects to have worn off. If sedatives have been used for a prolonged period or in large doses (e.g. with head injury) it may be difficult to decide whether these are still contributing to the depth of coma. Particular difficulty arises with highly lipid soluble drugs like thiopentone. A recent review suggests waiting five times the elimination half-life of the sedatives used (10); however this does not take into account the duration of infusion (i.e. context-sensitive half-life), altered pharmacokinetics with very high doses or the presence of active metabolites.

c) The use of antagonist agents may be useful. If muscle relaxants have been used, confirm that neuromuscular conduction is intact with a peripheral nerve stimulator. Administer the antidotes naloxone and flumazenil if opioids or benzodiazepines have been given and look for a change in brainstem reflexes.

d) Measurement of plasma concentrations of drugs should reveal drug concentrations below the therapeutic range e.g. alcohol in levels below the legal limit for driving. The median concentration of thiopentone permitting motor response is 12 mg/L (11) but there is considerable individual variation with levels as low as 4mg/L required in some individuals for return of motor response (11-12).

The exclusion of sedative agents as a contributing cause of coma may require considerable knowledge and experience. Ultimately the clinician must use their knowledge and judgement to decide whether or not to rely on brainstem testing alone to diagnose brain death.

If sedation may be contributing to the absence of brainstem reflexes then brain death cannot be diagnosed on clinical testing alone. The use of additional confirmatory tests (e.g. cerebral angiography) however may allow the diagnosis of brain death to be made (see Section D below).

e) Hypothermia as a cause of coma must be excluded. Core body temperature should be more than 35°C when clinical assessment of brain stem reflexes is carried out. If therapeutic hypothermia has been used, brain stem tests should be delayed until at least 24 hrs after return of normothermia

f) Metabolic or endocrine causes that may contribute to coma must be excluded. Hypothyroidism, pan-hypopituitarism, adrenal dysfunction, renal failure and hepatic failure can lead to a profound decrease in the level of consciousness.
The commonest metabolic abnormality in brain dead patients is hypernatraemia, often related to diabetes insipidus. Serum sodium should not be grossly abnormal; we recommend 125-155 mmol/L as the acceptable limits for brain stem testing. Similarly blood glucose, phosphate and magnesium levels should not be grossly deranged.

g) Severe hypotension precludes testing of brain stem reflexes. Blood pressure should be greater than 90mmHg systolic (MAP > 60mmHg) for brain stem tests. Infusion of fluid and vasoactive drugs may be needed to maintain blood pressure.

The diagnosis of brain death sometimes requires a complex clinical decision. In complicated cases and especially if a practitioner does not undertake brainstem tests often, we suggest getting advice from a Consultant in Intensive Care Medicine who undertakes brainstem tests on a regular basis.

(C) Formal clinical testing for Brainstem reflexes

The first formal examination can be undertaken when the patient fulfils the pre-conditions in A) and B) above and has been observed to have fixed pupils and absent cranial nerve reflexes for at least 4 hours.

(1) **No motor response** within the cranial nerve distribution in response to adequate stimulation of the trigeminal area and of the limbs. Absence of response to a painful stimulus applied peripherally could be the result of a high cervical injury, thus testing within the distribution of cranial nerves must always be performed. Trigeminal stimulation can be applied by pressure on the supraorbital notch or at the level of the tempero-mandibular joint.

(2) **No pupillary response to light.** A history of pre-existing abnormalities of the pupil or previous surgery to the eye (e.g. iridectomy) may influence interpretation of this test. Examine each eye with lights in the room dimmed and use a strong light. The pupils should be more than 4mm in diameter. The normal response is brisk constriction of the pupil. Round, oval or irregularly shaped pupils are compatible with brain death. In most brain dead patients pupils are in the mid position (4-6mm).

(3) **Corneal reflex.** Test the corneal reflex by touching the cornea with a wisp of cotton wool. If this fails to elicit a response a stronger stimulus is applied with for example, a sterile throat swab and firm direct pressure. Blinking of the eyelids is the normal response and both eyelids must be observed.

(4) **Oculovestibular reflex (caloric testing).** Before testing this reflex, both ears are inspected using an auroscope to confirm that the tympanic membrane is intact and the external auditory canal is not obstructed by wax or other material. A fractured base of skull resulting in blood, CSF or brain tissue in the external auditory canal is a contra-indication to performing the test on that ear. The patients head is placed in the

midline and elevated 30° from the supine position. This ensures that the lateral semi-circular canal is vertical, maximising the response. A soft catheter is introduced into the external auditory canal for gentle, slow irrigation with at least 50ml of iced water while the eyes are held open by an assistant. The eyes should be observed for a minute after irrigation is completed. There should be a 5 minute interval before repeating the test on the opposite side.

In an unconscious patient, an intact oculovestibular reflex causes tonic (slow) deviation of the eyes towards the irrigated ear. During testing to confirm brain death, any movement of one or both eyes, whether conjugate or not, excludes a diagnosis of brain death. When the reflex is absent the eyes remain fixed.

(5) **Oculocephalic reflex (Doll's eye phenomenon).** This test must not be performed in patients with an unstable cervical spine injury. The examiner holds the patient's eyes open and the head is turned suddenly from the middle position on both sides. When the reflex is intact the eyes turn opposite to the side of head movement as if lagging behind. The reflex is absent when the eyes move with the head and do not move within the orbit. If Test (4) above can be performed this test may be omitted.

(6) **Pharyngeal (gag) reflex.** A tongue depressor is used to stimulate each side of the oropharynx and the patient observed for any pharyngeal or palatal movement.

(7) **Laryngeal (cough) reflex.** A suction catheter is introduced into the endotracheal or tracheostomy tube to deliberately stimulate the carina. The patient is observed for any cough response or movement of the chest or diaphragm.

(8) **Apnoea test.** This test is an essential part of the diagnosis of brain death. It should be undertaken when all other brain-stem reflexes are absent. It may not be possible to perform the test in patients with a high cervical cord injury or in patients with poor respiratory function.. In such patients, determination of brain death by clinical tests will not be possible and additional confirmatory tests (e.g. cerebral angiography) may be needed to confirm brain death. (see item (D) below)

The three components of the test are:

(a) Disconnection from mechanical ventilation for long enough to allow arterial CO_2 tension to reach a critical point (causing acidaemia).
(b) Prevention of hypoxaemia during this period.
(c) Absence of spontaneous respiratory efforts during this period.

Ventilate the patient with 100% oxygen before the test to ensure pre-oxygenation. Check the patient's arterial blood gases. If the PaCO2 is outside normal limits adjust the ventilator until a normal PaCO2 for that patient (normally 4.8-5.8 kPa) is achieved. Disconnect the ventilator. Disconnecting the patient from the ventilator removes the chance of artefactual detection of breathing by the ventilator due to the cardiac impulse. Deliver oxygen via a C-circuit or via a narrow suction catheter inserted into the endotracheal tube.

Inspection of the reservoir bag will enable monitoring of respiration; visual inspection for chest and abdominal movement is also required. Visual inspection of the chest and abdomen typically show minimal movement synchronous with heart beat. At five minute intervals, the arterial blood gases are checked until the PaCO2 increases to 8.0 kPa or higher and associated acidaemia has developed (pH<7.30) (10). If the patient has a history of chronic respiratory disease, allowance must be made for decreased sensitivity to a high PaC02. Occasionally it takes more than 10 minutes for the required changes in PaCO2.

The apnoea test may lead to instability in the patient's condition and deaths have occurred during this procedure. Maintain oxygen saturation levels within the normal range. Application of CPAP may maintain oxygenation without compromising recognition of respiratory effort. A Valsalva effect or barotrauma may occur if the expiratory valve is closed or if oxygen flows are too high through a suction catheter. If hypotension occurs vasopressors may need to be increased.

If, despite hypercarbia and acidaemia, there is no attempt at spontaneous respiration, the test is consistent with brain death.

More detailed descriptions of the clinical tests of brainstem function are available if required (5-10)

Spinal reflexes. Body movements, secondary to spinal cord reflexes, are sometimes observed after brain death. These may persist until asystole occurs. These movements represent only spinal cord activity as evidenced by the consistent clinical documentation of brain death in such patients with confirmation by an isoelectric electroencephalogram or the absence of intracranial blood flow. Movements noted include abduction or adduction of the arms, leg movements, head rotation (due to cervical muscle activity) and even a brief movement of the body to sit up to 45° (Lazarus sign). There is no facial movement in this situation however. A prospective study of 38 patients with brain death, mostly young adults, found a 39% frequency of spinal-generated movements (13).

(D) Situations where a diagnosis of Brain Death is not possible using clinical criteria alone:

The diagnosis of brain death by clinical examination leads to withdrawal of ventilatory support and cardiac death. Thus it is extremely important that the preconditions for testing are fulfilled and that an adequate number of clinical tests (to include apnoea testing) confirm absence of brainstem function.

Severe head and facial injuries can make it impossible to test all the brainstem reflexes. They may affect the ability to test pupillary and corneal reflexes, through periorbital swelling or direct eye injury. Likewise they may preclude testing the oculovestibular reflex, because of CSF otorrhoea or occlusion of the external auditory canal. There is no reported consensus on the minimum number of brainstem reflexes, that must be tested although apnoea testing is seen as essential. The Australian Guidelines contain a useful rule of thumb that you must be able to test 'at least one eye and at least one ear' (10).

Brain death is a clinical diagnosis. Clinicians must use their clinical judgement in conjunction with formal guidelines in assessing whether the pre-conditions are fulfilled and whether sufficient brainstem tests can be performed to diagnose brain death.. You must be in a position to justify the diagnosis of brain death if asked to do so subsequently. If not, you should not diagnose brain death on the basis of brainstem tests.

When there are limitations to the clinical tests which can be undertaken the diagnosis of brain death may still be possible if confirmatory tests are used. Confirmatory tests may also enable the diagnosis to be made in patients who do not fulfil the pre-conditions e.g. those who have received large doses of sedative agents.

If the pre-conditions for clinical determination of brain death are not met or if insufficient clinical tests can be performed, brain death cannot be diagnosed using clinical examination alone. It may then be appropriate to support the clinical signs suggestive of brain death by using an appropriate ancillary test.

Ancillary tests for brain death

Tests to confirm the findings of clinical tests for brain death rely on demonstrating the absence of parenchymal blood flow in the brain.

1. Four vessel cerebral angiography that demonstrates absence of intracranial blood flow is the 'gold-standard' ancillary test to confirm a diagnosis of brain death (6-7, 10-12). This aid to diagnosis of brain death is only possible in specialist centres where cerebral angiography is available. There is a detailed description in the Australia-New Zealand guidelines (10).
2. Radionuclide imaging with Tc-99m HMPAO (other radionuclides do not cross the blood brain barrier).

3. CT angiography (CTA) is commonly used although not as widely accepted and there are potential pitfalls in interpretation; see the US and ANZICS Guidelines for details (8, 10). Protocols are in existence particularly in France since 1998 and a formal protocol may be useful (14).

Significant false-negative rates have been reported with CTA i.e. filling of cerebral blood vessels in patients who fulfil clinical criteria for brain death (15). However there have been no reports of CTA suggesting brain death (i.e. absent opacification of intracranial vessels) in patients who do not fulfil clinical criteria for brain death. No formal studies of CTA in comatose patients who are not brain dead have been published.

Individual Intensive Care Medicine specialists and radiologists should decide on a case-by-case basis whether to rely on CTA to confirm brain death. A recent Irish review is a useful overview (16).

EEG, MRI and Transcranial Doppler are not recommended as reliable tests to confirm a diagnosis of brain death.

All authorities agree that ancillary tests should be used in combination with clinical tests (rather than as stand-alone tests) to diagnose brain death. This is to avoid the possibility of a patient being declared brain dead while not fulfilling clinical criteria.

Declaration of death.

It is standard practice to repeat the tests described in (C) to confirm the absence of brainstem reflexes. When organ donation is being considered, this is regarded as essential. A 'reasonable' period of time should intervene between the two sets of tests (although no specific minimum time period has been recommended (3, 10, 12).
The apnoea test is the final test to be done. If it is positive for the second time, the patient should then be declared dead and the time and date noted. This is the time of death. Many critical care units use a check list to be completed by the doctors concerned. An example of such a list is appended.

There is no documented case of a person who fulfils the preconditions and criteria for brain death subsequently regaining consciousness.

Who should do the tests?

Two sets of tests should be undertaken by different doctors; one a consultant, the other a doctor fully registered for at least five years and engaged in acute patient care in hospital. If organ donation is being considered, the doctors certifying brain death should not be involved in any proposed transplant procedure.

Communication, organ donation and other considerations

If the first set of formal tests show no sign of brain stem activity, it is advisable to inform the family of the findings and that confirmation of these findings on second testing (which is anticipated) will lead to a diagnosis of brain death.

As brain death provides the opportunity to donate organs for transplantation and given the need of patients on transplant waiting list for donated organs, it is important for clinicians, usually the Intensive Care team, to inform the family sensitively that this option is likely to arise.They may be asked to begin to consider what the patient would have wished in relation to organ donation.

Contact with the transplant co-ordinator may be warranted as a request for organ donation would be pointless if the patient is not suitable as an organ donor. It is reasonable to undertake this after the first set of tests. In many cases in whom brain death is diagnosed the circumstances of the brain injury make it mandatory to report the death to the Coroner (as per Coroner's Guidelines). In such cases the Coroner must be informed and permission requested for organ retrieval for transplantation. The Coroner normally grants permission for this but usually requires a post-mortem examination and may wish to place limitations on transplant procedures. Families should be advised of the role of the Coroner in these cases.

If organ donation is not to take place, then a time should be set to withdraw ventilation, Most families prefer to be in attendance while cessation of circulation occurs – usually over 10 - 20 minutes. Privacy and religious or other ceremonies should be facilitated as much as possible during this time.

References:

(1) **Pallis C.** Prognostic significance of a dead brainstem. *British Medical Journal* 1983; 286: 123-4

(2) Diagnosis of Brain Death & Medical Management of the Organ Donor 2010. Intensive Care Society of Ireland https://www.anaesthesia.ie/attachments/article/92/ICSI%20Guidelines%20MAY10.pdf

(3) **Irish Working Party on Brain Death.** Memorandum on Brain Death (1988). *Irish Medical Journal* 1988; 81: 42-5.

(4) **Dobb GJ, Weekes JW.** Clinical confirmation of brain death. *Anaesthesia and Intensive Care* 1995; 23: 37-43

(5) **Intensive Care Society (UK).** Guidelines for Adult Organ and Tissue Donation 2005. p 30-34. www.ics.ac.uk (see Standards and Guidelines, Organ and Tissue Donation)

(6) Gardiner D, Shemie S, Manara A, Opdam H. International perspective on the diagnosis of death. British Journal Anaesthesia 2012 :108 (S1): i14–i28

(7) Academy of Medical Royal Colleges. A Code of Practice for the Diagnosis of Brain Stem Death. London: Department of Health, 1998.

(8) **Australia and New Zealand Intensive Care Society.** ANZICS Statement on Death and Organ Donation. 2013 http://www.anzics.com.au/Downloads/ANZICS%20Statement%20on%20%20Death%20and%20Organ%20Donation%20Edition%203.2.pdf

(9) **Shemie SD, Doig C, Dickens B, et al.** Severe brain injury to neurological determination of death: Canadian forum recommendations. *Canadian Medical Association Journal* 2006; 174: S1-13

(10) Wijdicks EF, Varelas PN, Gronseth GS, Greer DM. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010; 74: 1911–8

(11) **Cordato DJ, Herkes GK, Mather LE, et al.** Prolonged thiopentone infusion for neurosurgical emergencies: Usefulness of therapeutic drug monitoring. Anaesth Int Care 2001; 29:339-348

(12) **Saito T, Kurashima A, Oda T et al.** [Quantitative analysis of plasma concentration of barbiturate for diagnosis of brain death] No Shinkei Geka-Neurological Surgery 2002; 30: 593-**9**

(13) **Saposnik G, Bueri JA, Maurino J, et al.** Spontaneous and reflex movements in brain death. Neurology 2000;54:221-3

(14) **Frampasa E, Videcoqb M, de Kervilerc E, et al**. CT Angiography for Brain Death Diagnosis *AJNR 2009 30: 1566-1570.* http://www.ajnr.org/content/30/8/1566.full

(15) **van der Lugt A.** Neuroradiology. Imaging tests in determination of brain death. Neuroradiology 2010; 52: 945–947 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2952109/

(16) **Murray TÉ, Brennan P, Looby S.** The role of imaging in anoxic brain injury and brain death: a review of modalities with an Irish and international perspective. Ir J Med Sci (2015). doi:10.1007/s11845-015-1293-6

CHECKLIST FOR CLINICAL DIAGNOSIS OF BRAIN DEATH (ICSI 2016)

Name_____

Address_____

_____

Date of birth _____

Condition which led to irremediable brain damage: _____

Onset of apnoeic coma; Date ☐ Time ☐

PRECONDITIONS; ***is apnoeic coma due to any of the following?***

	Assessment A		**Assessment B**	
	Yes	No	Yes	No
Depressant drugs	☐	☐	☐	☐
Neuromuscular blocking drugs	☐	☐	☐	☐
Hypothermia	☐	☐	☐	☐
Metabolic causes	☐	☐	☐	☐
Endocrine disturbance	☐	☐	☐	☐

CLINICAL TESTS OF BRAIN STEM FUNCTION:

	Assessment A		**Assessment B**	
	Yes	No	Yes	No
Is there a motor response to painful stimulus in cranial nerve distribution?	☐	☐	☐	☐
Do the pupils react to light?	☐	☐	☐	☐
Are corneal reflexes present?	☐	☐	☐	☐
Do the eyes move on caloric testing?	☐	☐	☐	☐
Is there a gag reflex?	☐	☐	☐	☐
Is there a cough reflex?	☐	☐	☐	☐
Were there respiratory movements during apnoea testing?	☐	☐	☐	☐
PaC02 pre and post apnoea test; Pre	☐ Post	☐	Pre ☐ Post	☐
pH pre and post apnoea test; Pre	☐ Post	☐	Pre ☐ Post	☐

Date and time of tests: Assessment A ☐ Assessment B ☐

	Assessor(s) A	**Assessor(s) B**
Name(**s**)		
Grade		
Signature		

Confirmation of brain death

Do the above tests confirm brain death? Yes ☐ No ☐

Date of death ☐ Time of death ☐

Name ☐ Signature ☐ Grade ☐