Brain Stem Death

Historical overview

Historically, death was believed to occur at the moment that all vital signs ceased permanently. For scientists, death in the past coincided with the permanent arrest of all bodily functions. Since the mind is the expression of brain functions, the cessation of its activity was assumed as part of the physical effects of death. For the philosophers and religions, death signifies the departure of the soul and the mind alongside with the cessation of the bodily functions.

Death causes the irreversible loss of those essential characteristics which are necessary to the existence of a living human being. Thus, the definition of death should be considered as the irreversible loss of the capacity of consciousness combined with irreversible loss of the capacity to breathe.

Death took a different meaning after the mechanical ventilation was invented and patients with catastrophic brain injury were supported in hospitals. This drastic intervention created a new state. In this comatose state, the brain function came to an end, but the rest of the bodily functions were supported by intensive care interventions.

One of the earliest references (1902) of the concept of brain death was made by H. Cushing when he described a patient that was maintained alive by artificial ventilation for 23 hours. The landmark article (1959) by Mollaret and Goulon (neurologists), was an extension of previous anecdotal cases. The authors presented a case series of 23 patients with a new type of coma: “coma dépasse”. This neurological state was associated with complete absence of cognitive and vegetative functions, which went beyond the deepest comas so far described.

Despite the ethical dilemmas that this observation generated, the authors managed to describe clearly what is nowadays called “brain death”. This included the neurological (clinical and electroencephalographical (EEG)) description as well as observations of diabetes insipidus, cardiovascular instability, hormone derangement and neurogenic pulmonary oedema. Later reports of “coma dépasse linked this neurological state with lack of cerebral blood flow.

In 1968, the report of the Ad Hoc Committee of the Harvard medical school followed, “defining irreversible coma as a new criterion for death”. This state of coma had the characteristics of unreceptivity and unresponsivity, absence of breathing and absence of brain stem reflexes.

Later, in 1971, Mohandas and Chou (neurosurgeons) published the Minnesota code of Brain Death Criteria. Their definition included specific time of apnoea (4 minutes of disconnection), the need for exclusion of metabolic factors, longer observation time (12 hours) and the known cause of irreparable intracranial damage. Most importantly they introduced that the irreversible damage of the brain stem was a critical component.

In 1976 the conference of Royal colleges and faculties in United Kingdom (UK) published the memorandum on brain death. This later (1995) changed to brain stem death and UK’s position was: “if the brain stem is dead, the brain is dead, and if the brain is dead, the person is dead”.

Since then, relevant professional bodies have published criteria for confirmation of death with neurological criteria, describing the conditions under which the diagnosis should be made.

The incentive of diagnosing death using neurological criteria was derived by the need for defining futility and finding a way to help physicians to withdraw support in cases that the damage of the brain is irreversible rather than the need to facilitate organ transplantation.

Brain stem death or whole brain death?

There are differences of the definition of death in different countries even when we apply neurological criteria. In many countries, the neurological criteria include the irreversible cessation of the function of the whole brain including the brain stem. Most of these countries require the use of confirmatory tests such as EEG or demonstration that the cerebral blood flow has ceased. In contrast, there are also countries that align the concept of brain death with that of brainstem death. In United Kingdom (UK), this definition exists and is used since 1995. In these cases, confirmatory tests are not required.

Clinical examination

Although the clinical examination, who is performing it, how and when vary in each country, there are common principles that should be followed in order to reach a safe and correct diagnosis. The clinicians involved should be senior and competent, and the tests should be repeated twice by two different clinicians. Although the specialty of the clinicians is not strictly specified, they should not be members of the organ procurement or transplant teams.

Preconditions: the patient should be in deep coma, totally unresponsive and apnoeic (ventilator dependent). There should be no doubt that the coma is due to irreversible brain damage. The underlying cause of the coma should be known.

Exclusions: confounding conditions or reversible causes of the coma and/or the absence of brain stem activity/ reflexes should be excluded.

Temperature: primary hypothermia as the cause of unconsciousness should be excluded. Although brain stem reflexes are abolished if temperature falls below 28°C, temperatures between 32-34°C are occasionally associated with impaired levels of consciousness. In clinical practice, it is recommended the temperature to be above 34°C at the time of the assessment. The effects of hypothermia on the central nervous system (CNS) are totally reversible when temperature is corrected to normothermia.
<table>
<thead>
<tr>
<th>Core temperature</th>
<th>CNS</th>
<th>Neuromuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-32°C</td>
<td>Apathy, dysarthria, impaired consciousness</td>
<td>Increased muscle tone, shivering, ataxia</td>
</tr>
<tr>
<td>32-28°C</td>
<td>Hallucinations, reduced consciousness, pupillary dilatation</td>
<td>Hyporeflexia, rigidity</td>
</tr>
<tr>
<td>&lt; 28°C</td>
<td>Coma, impairment of brainstem auditory evoked potentials absent corneal reflex, absent bulbar reflex</td>
<td>Areflexia</td>
</tr>
</tbody>
</table>

**Table 1: Effects of temperature on CNS and neuromuscular coupling**

**Drugs:** It is essential to review the history of drug administration or drug ingestion prior to brain stem testing. The presence of drugs and toxins that can either cause reversible coma or mimic brain stem death should be excluded (history, toxicology screening). Barbiturates and tricyclic antidepressants in particular can cause neurological states similar to brain stem death. The effects of sedative drugs on the CNS can be prolonged in the presence of hypothermia, renal or hepatic failure. In addition, lipophilic drugs are cumulative when used as prolonged infusions.

The time between discontinuation of CNS depressant drugs and safe brain stem testing is difficult to be determined and depends on the pharmacokinetics of the drug, the length of infusion, total dose, the renal and hepatic metabolic function, normothermia and prior use of therapeutic hypothermia. A safe calculation is by using five times the drug’s half-life but also taking into account the factors above. When possible, plasma levels should be measured. It is not recommended to perform brain stem test if thiopentone plasma levels are >5mg/L, or midazolam levels are >10μg/L. Levels of alcohol below the legal driving limit are considered safe. The presence of muscle relaxants should be also excluded by reviewing the drug administration and with a peripheral nerve stimulator.

**Metabolic:** Severe endocrine, metabolic and electrolyte abnormalities may impair consciousness and CNS function or may give indication of ingestion of substances that may be missed on drug/toxic screen. Some electrolytes although do not have an effect on CNS may impair neuromuscular transmission and cause myopathy and in extreme low levels even flaccid quadriplegia. However, brain stem death is accompanied by metabolic and electrolyte imbalance and aiming for normal range values maybe unrealistic. Throughout the clinical examination, mean arterial pressure should be maintained >60mmHg (UK guidelines) or systolic blood pressure should be >100mmHg (American guidelines). The UK code of practice has given safe range of electrolytes for brain stem testing as guidance.
Electrolyte Safe range for brain stem testing

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Safe range for brain stem testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>115-160 (mmol/L)</td>
</tr>
<tr>
<td>Potassium</td>
<td>&gt;2.0 (mmol/L)</td>
</tr>
<tr>
<td>Glucose</td>
<td>3.0 – 20 (mmol/L)</td>
</tr>
<tr>
<td>Phosphate</td>
<td>&gt;3.0 (mmol/L)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>&gt;0.5 (mmol/L)</td>
</tr>
</tbody>
</table>

*Table 2: Safe electrolyte range for performing brain stem testing*

**Other causes of apnoea:** the ventilator settings should be carefully reviewed, and appropriate levels of ventilator sensitivity should be set. The presence of neuromuscular blocking agents should be excluded (use of peripheral nerve stimulator). Severe neuromuscular disorders that can that can abolish brain stem reflexes should be excluded. Establishing a clear diagnosis of irreversible brain damage before brain stem testing is paramount.

Head injuries are commonly associated with cervical spinal injuries. High level cervical spinal injuries can cause central apnoea, and, in these cases, ancillary testing should always be performed.

<table>
<thead>
<tr>
<th>Levels</th>
<th>Valid apnoea test</th>
<th>Rational</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁-C₃</td>
<td>No Ancillary tests are needed</td>
<td>Ascending oedema can reach the level of medulla and cause central apnoea.</td>
</tr>
<tr>
<td>C₄-C₆</td>
<td>CAUTION Ancillary tests are highly recommended</td>
<td>Phrenic nerve originates from C₄. There are case reports of central apnoea even with injuries at C₅ level.</td>
</tr>
<tr>
<td>C₆-T₁</td>
<td>Yes Apnoea test is not affected.</td>
<td></td>
</tr>
</tbody>
</table>

*Table 3: Levels of spinal cord injury and validity of apnoea test*

**Brain stem clinical examination**

The absence of the following brain stem reflexes should be confirmed. Clinical examination should proceed only if the preconditions have been met and confounders have been carefully excluded.

- Pupillary response to light (sensory II, motor III)
  - The direct and indirect response to bright light should be absent in both eyes.
- Corneal reflex (sensory V, motor VII)
  - There is no corneal reflex when the cornea is touched with a cotton swab (inability to blink).
- Oculovestibular response (sensory VIII, motor III, VI)
  - There are no eye movements during or after the injection of 50mls of ice cold water into the external auditory meatus. The patency of the canal should be first confirmed by direct inspection. The head should be elevated to 30° and the injection of the water should be over 1min. Observation should be excluded delayed response (after the injection)
- Motor response to supraorbital pain (sensory V, motor VII)
  - There should be no facial grimacing or limb movement in response to supraorbital pressure.
- Cough and gag reflex (sensory IX, motor X)
There should be no cough reflex during bronchial suctioning or gag reflex during stimulation of the posterior larynx with a spatula or Yankauer suction tip.

Apnoea

Performance of apnoea testing should be reserved as the last test of brainstem function. There are variations of how to perform the apnoea test internationally. The principles though are the same. The CO\textsubscript{2} should rise abruptly from a predetermined baseline in order to result in a decrease of the cerebrospinal fluid’s pH which triggers the respiratory centres in the medulla oblongata. To achieve this, the patient is disconnected from the ventilator, and oxygenation is maintained via either an endotracheally placed catheter connected to an oxygen flowmeter (flow 2lt/min) or application of continuous positive airway pressure (CPAP) via a T-piece with an adjustable pressure limiting valve. During the test, the patient is observed continuously for any respiratory effort. At the end of the test, the patient is reconnected to the ventilator and ventilated in order the CO\textsubscript{2} to reach pre-test values.

Any respiratory muscle activity (including accessory muscles) is considered as breathing effort and the test should be stopped at that point. In this case, brain stem death is precluded. The apnoea test should be aborted if oxygen saturation is persistently <85% during the apnoea test. In patients with chronic CO\textsubscript{2} retention apnoea test should be commenced after the CO\textsubscript{2} is raised to a level that causes a mildly acidotic pH.

The legal time of death is the time of the conclusion of the first set of tests for determination of brain death. In countries that two tests are a requirement there is no specific timeframe between the two sets of clinical tests. In USA is recommended to wait 6 hours between the two sets of tests.
<table>
<thead>
<tr>
<th>Country</th>
<th>Apnoea test</th>
<th>Time of observation: 5min</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>Pre-oxygenate the patient with 100 per cent oxygen. Maintain SpO₂ &gt; 95%, reduce minute ventilation to raise CO₂. Confirm that the PaCO₂ is at least 6.0KPa and pH is less than 7.40. After disconnecting the patient from the ventilator deliver oxygen via an endotracheal catheter with flow of 5L/min. Observe for 5min. PaCO₂ should have an increase of more than 0.5KPa from starting PaCO₂. Aim: starting PaCO₂ ≥ 6.0KPa and pH &lt; 7.40 PaCO₂ should rise &gt; 0.5KPa</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>Pre-oxygenate the patient with 100 per cent oxygen for at least 5 minutes. Mechanically ventilate to mild hypercarbia (PaCO₂ ~ 45 mmHg [6 KPa]) before disconnecting the patient from the ventilator. Disconnect the patient from the mechanical ventilator. At the end of the period without mechanical ventilation, apnoea must persist in the presence of an adequate stimulus to spontaneous ventilation, i.e. an arterial PaCO₂ &gt; 60 mmHg (8 kPa) and an arterial pH &lt; 7.30. If starting from normocapnoea, the PaCO₂ is likely to be &gt; 60 mmHg (8 KPa) after 10 minutes. Aim: PaCO₂ &gt; 60mmHg (8 kPa) Time of observation: not clearly defined</td>
<td></td>
</tr>
<tr>
<td>United States of America (USA)</td>
<td>Pre-oxygenate the patient with 100 per cent oxygen for at least 100% oxygen to a PO₂ &gt; 200mmHg. Reduce minute ventilation to normocapnia. Maintain SpO₂ &gt; 95%, obtain baseline arterial blood gas. Disconnect the patient from the ventilator. Preserve oxygenation via insufflation catheter through the endotracheal tube and deliver 6L/min oxygen. Look closely for respiratory movements for 8-10 minutes. If no respiratory effort is observed repeat arterial blood gas after 8min. If the PaCO₂ &gt; 60 mmHg the test supports the clinical diagnosis of brain death. Aim: PaCO₂ &gt; 60mmHg (8 kPa) Time of observation: 8-10min up to 15min if needed</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>It is recommended that a PaCO₂ &gt; 60mmHg be achieved to ensure that an adequate stimulus is presented to the respiratory centre. The arterial or capillary blood pH should be &lt; 7.28 by the end of the apnoea test. An initially normal PaCO₂ before apnoea testing is begun (40 ± 5 mm Hg). Preoxygenation with 100% oxygen allowing a PaO₂ &gt; 200mmHg. During the apnoea test, it is suggested that 100% oxygen is delivered via a cannula placed in the trachea, or at the level of the carina, while the ventilator is stopped. The arterial PaO₂, PaCO₂ and pH should be checked at 8-10 minutes. The apnoea test is positive if no respirations are observed over the 8-10 minutes, provided that the PaCO₂ rises to greater than 60 mm Hg. Aim: PaCO₂ &gt; 60mmHg PaCO₂ should rise &gt; 20mmHg pH ≤ 7.28 Time of observation: 10-15min</td>
<td></td>
</tr>
</tbody>
</table>

*Table 4: Variations of apnoea test*
Ancillary testing

Brain death is a clinical diagnosis. Confirmatory tests are not mandatory in all countries. In all cases, ancillary testing to determine absence of intracranial flow or electrical brain function is indicated when comprehensive neurological examination cannot be reliably performed or evaluated (extensive maxillofacial injuries, high cervical spinal injuries, when pharmacological or metabolic cofounders exist). Ancillary testing does not eliminate the need for carrying out the clinical tests by two physicians to the extent possible. None of these ancillary tests can replace the clinical examination and none give conclusive answers.

Cerebral angiography: When intracranial pressure exceeds arterial perfusion pressure, causes cerebral-circulatory arrest. A selective 4 vessel cerebral angiogram allowing to visualise both anterior and posterior is considered the gold standard of the ancillary tests. External carotid circulation should be evident and there should be no intracerebral filling at the level of the carotid bifurcation or circle of Willis. Filling of the superior sinus may be present. The reliability of cerebral angiography is very good but it requires expertise that may be available only in neuroscience units, requires transporting a potentially unstable patient to the radiology department and is an invasive technique with potential serious complications.

Radionuclide Imaging Techniques: the most common tracer used is the Tc-99m hexamethylpropylene-amine oxime (Tc-99m HMPAO), is lipid soluble, crossing the blood-brain barrier, providing information on arterial cerebral blood flow and uptake of tracer within perfused brain tissue. The absence of isotope uptake produces a characteristic “hollow skull” phenomenon while increased extracranial flow may result in enhancement of the nose (“hot none sign”). This picture supports the diagnosis of brain death. The sensitivity of the technique improves with repetition of the test within 24-48 hours.

Transcranial Doppler ultrasonography: this technique requires substantial clinical experience but the advantages are its portability and non-invasiveness. It should be noted that absence of Doppler signals does not necessarily mean lack of cerebral flow as 10%-25% of patients do not have trans-temporal windows. In brain death, the typical picture is systolic spikes or oscillating flow in any cerebral artery. Posterior and anterior circulation should be examined.

Electroencephalography: Electroencephalography (EEG) has long been used as a supplementary test for brain death. In some countries remains mandatory despite its lack of accuracy. The sensitivity and specificity of the technique is reported around 90% with up to 20% false-negative results. It should be noted that although EEG can detect cortical activity it cannot exclude or confirm deeper cerebral or brainstem function. Hypothermia, metabolic abnormalities, drug presence and electrical interference is some of the limitations. In Canada is no longer recommended as an ancillary test.

Somatosensory evoked potentials: both brain stem auditory evoked potentials (BAEP) and somatosensory evoked potentials (SSEP) have been used as ancillary tests. While the early components of BAEPs and SSEPs are minimally affected by sedative drugs, hypothermia, drugs, and metabolic derangements can affect middle and late somatosensory and auditory potentials.
False-positive (patient does not meet the clinical criteria for brain death) results have been recorded with transcranial Doppler, radionuclide imaging and CT angiogram. This emphasises the importance of a robust clinical diagnosis.

Red flags and challenging cases

Time of testing
Although not all of the countries have a set timeframe between loss of brainstem reflexes and clinical testing. Most professional bodies recommend waiting between 4-6 hours from the time of the loss of the last brainstem reflex.

When the cause of death is anoxia, it is recommended waiting 24 hours before testing.

In cases that therapeutic hypothermia was used (out of hospital cardiac arrest) it is advised the tests to be performed 24 hours after rewarming to normothermia.

Isolated brain stem pathology
Acute irreversible neurological injury may be confined to the brain stem (pontine haemorrhage, basilar artery embolic stroke, gunshot wounds). In these cases, the rest of the brain may initially not be affected until obstructive hydrocephalus develops that in turn will cause increased intracranial pressure. Longer observation periods are recommended in these cases (German guidelines suggest 72 hours of observation). The clinical confirmation is adequate and the use of ancillary tests may confuse the picture as cerebral blood flow may be maintained and EEG may show non-reactive alpha or spindle patterns.

Neuromuscular disorders
They have been reported severe cases of Guillen Barre syndrome that resemble brain stem death. It is important to establish a clear cause of the irreversible damage to the brain before undertaking clinical examination of the brain stem.

Pathophysiologic changes during brain stem death

In high intracranial pressure states, herniation of the diencephalon, compresses the pituitary stalk against the diaphragma sellae. If the pituitary gland itself is damaged, the posterior lobe is usually involved while the anterior lobe is spared as it is protected within the sella turcica. In addition, the anterior pituitary lobe of the basal part of hypothalamus is normally perfused by extradural blood supply (cavernous portion of carotid artery). These mechanisms explain why after coning, diabetes insipidus is observed in the majority of brain dead patients (65%) but not all and why the anterior part of the pituitary gland may still work despite the lack of intracranial blood flow. Diabetes insipidus causes sudden free water loss and results in intravascular depletion, hypernatraemia, hypotension and cardiovascular instability.

In abrupt increases of intracranial pressure, a massive outflow of catecholamines occurs. This catecholamine surge has a negative effect on the myocardium. ECG changes vary from increased ST segments, inversion of T waves, widening of QRS complexes to QT interval prolongation. Echocardiographically, there is evidence of decreased ejection fraction, and a plethora of wall motion abnormalities. These abnormalities may reflect reversible or irreversible myocardial injury.
The hypotension that follows the high catecholamine state of brain stem death, is probably caused by the autonomic uncoupling leading to the loss of the baroreceptor sensitivity and the loss of the heart rate variability. In addition, loss of spinal cord sympathetic activity due to herniation through the foramen magnum causes vasodilatation.

Neurogenic pulmonary oedema has been observed after neurological catastrophes. The exact mechanism is not fully understood. It seems to be a combination of increased pulmonary vascular permeability and increased capillary hydrostatic pressure.

<table>
<thead>
<tr>
<th>Theoretical mechanisms of neurogenic pulmonary oedema formation</th>
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<tbody>
<tr>
<td><strong>Pulmonary vascular permeability</strong></td>
</tr>
<tr>
<td>• Increased protein pulmonary oedema fluid</td>
</tr>
<tr>
<td>• Neuropeptide Y, alpha adrenergic agonists, pulmonary microvascular injury from rapid increase of in pulmonary pressure, inflammatory mechanisms</td>
</tr>
<tr>
<td><strong>Pulmonary hydrostatic pressure</strong></td>
</tr>
<tr>
<td>• Pulmonary venous constriction</td>
</tr>
<tr>
<td>• Increased systemic venous constriction and increased venous return</td>
</tr>
<tr>
<td>• Failure of left ventricle (direct myocardial injury, myocardial stunning, increased systemic afterload, increased vagal tone)</td>
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</table>

Coagulation abnormalities are present few days after brain stem death either due to the release of plasminogen activator and thromboplastin from the injured/necrotic brain or the effect of the catecholamines on platelet function.

Because of the physiological instability that follows brain death it is sometimes challenging to maintain the levels of homeostasis that is required to perform a valid clinical examination. Some hospitals have introduced “catastrophic brain injury protocols” in order to maintain physiology until the brain stem tests are performed. Robust brain stem testing is important as eliminates all possible doubt about survivability while minimises the suffering of the family as it confirms the diagnosis of death in a timely manner.
Catastrophic Brain Injury Care Pathway

Do you suspect brain stem death? Yes/No
Are pupils fixed and dilated and GCS 3/15 Yes/No
Is the patient apnoeic (not triggering ventilator)? Yes/No
Are cough and gag reflexes absent? Yes/No
Has a decision to stop neuroprotection been made? Yes/No

If ‘Yes’ to all of above questions please commence the following checklist.

Time starting the protocol: ............... Page Specialist Nurse on Organ Donation: 07659100103 (time: )

**Ventilation Nurse and NICU Dr**

**Targets:**
- $pO_2$: 8-14 kPa
- $pCO_2$: 5-6.5 kPa

**Additional Actions:**
- Sit up the patient at an angle of approx 30° - 45° and turn hourly
- Recruitment manoeuvre by medical team to optimise lung ventilation (eg. CPAP mode 25-40 cm H$_2$O for 30-50 secs)
- Set PEEP 8-10 cm H$_2$O
- Lung Protective ventilation (TV 6-8ml/kg, Peak pressure ≤30cm H$_2$O)
- Repeat recruitment manoeuvre if $pO_2$ ≤ 10.0kPa
- Review ventilation 2 hourly – repeat recruitment manoeuvre if deteriorating

**Circulation Nurse & NICU Dr**

- Insertion of Central Line
- Calibrated LIDCO (Please record LIDCO number: ....)
- Start cardiovascular algorithm (time: )

**Renal and Electrolytes**

**Targets:**
- Urine output 0.5-2.5ml/kg/hr
- Na 125-150mmol/L
- K+ 4.0-5.5mmol/L
- Mg > 0.8mmol/L
- Ca ionised 1.0-1.3mmol/L

**Additional Actions:**
- If polyuria (>300mls/hr for 2 hours) ensure adequate volume replacement
- If DI, bolus DDAVP 0.5mcg - consider vasopressin infusion if not started
- If oliguria, despite optimisation of CVS, consider Dobutamine/Dopamine

**Hormones and Haematology**

**Targets:**
- BMI 4.0 - 9.0 mmol/L
- Hb ≥ 8g/dl, Plt ≥ 50 x 10$^9$/L
- INR ≤ 2.0, APTT < 1.5, Fb ≥ 2.0g/L
- Temperature 35.5 – 37.5

**Additional Actions:**
- Start Insulin at one unit per hour and titrate to achieve BM control of 4-9mmol/L. If hypoglycaemia, continue Insulin and supplement with 20% dextrose – do not stop insulin altogether
- Continue enteral feed at low volume (10-30mls/h)

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**Figure 1: Catastrophic brain injury pathway- St. George’s University Hospitals NHS Foundation Trust, London, UK**
References