When brainstem death was formally defined by the Conference of Medical Royal Colleges and their Faculties in the UK in 1976, a concept, as well as a description of a pathological process, was introduced into medical practice. This article describes core anatomy, pathophysiology of brain injury, the process of testing within the current guidelines and briefly explores the ethical and legal issues inherent in the concept.

Cerebral anatomy

Although the brainstem is the anatomical link between cerebral hemispheres and spinal cord, its role exceeds that of simple conduit. This complex mass of nerve fibres and cells, nuclei and physiological centres exercises independent functions, the most fundamental being the maintenance of spontaneous ventilatory effort. Knowledge of both anatomy and function is important in understanding the mechanisms and manifestations of brain injury, the process of brainstem testing and the key concept that brainstem death is incompatible with consciousness.

From an embryological perspective, the brain develops from expansions of the neural folds into three primary cerebral vesicles separated from each other by constrictions: (i) the prosencephalon or forebrain, consisting of the diencephalon (thalamus and hypothalamus) and the paired cerebral hemispheres; (ii) mesencephalon or midbrain; and (iii) rhombencephalon or hindbrain consisting of the pons, medulla oblongata and the cerebellar hemispheres. The brainstem is a functional rather than anatomical unit and comprises the midbrain, pons and medulla. A mid-sagittal view of the brain is shown in Figure 1.

Key points

Brainstem death is irreversible and defines ongoing active support as futile.

For the purposes of organ retrieval, brainstem death is considered equivalent at law to death.

Meeting preconditions may be difficult but the published UK guidelines for brainstem death testing should be followed.

Confirmatory tests may help if continuing effects of sedatives cannot be excluded.

Communication with relatives is particularly important.
Midbrain

The midbrain connects the forebrain and the hindbrain, passing through the notch of the tentorium cerebelli. It is divided into two lateral halves known as the cerebral peduncles, each consisting of the crus cerebri, substantia nigra and the tegmentum. The crura cerebri contain descending fibres of the corticospinal, corticobulbar and corticopontine tracts.

Posterior to the cerebral aqueduct (central cavity connecting the third and fourth ventricles) are the four swellings of the tectum. The two superior colliculi are concerned with visual reflexes and the inferior colliculi relay auditory responses. Between the two superior colliculi lies the pineal gland, attached by a stalk to the posterior wall of the third ventricle.

Pons

The pons creates a prominent bulge between midbrain and medulla, demarcated from the latter by a transverse furrow in which the VI, VII and VIII cranial nerves run (Fig. 2). In addition to the ascending and descending tracts and cranial nerve nuclei, the pons contains the reticular nuclei which play an essential role in mechanisms of sleep, arousal and pain transmission.

Medulla oblongata

The medulla oblongata is conical in shape, continuous cranially with the pons and narrower caudally where it becomes continuous with the spinal cord at the level of the atlas. As well as the lower cranial nerves, olivary, gracile and cuneate nuclei, the medulla contains centres for cardiorespiratory control.

Brainstem function

It can be seen that the brainstem plays a vital role in the transmission of somatic sensory, special sensory and motor impulses, acting as a relay station between higher cortical centres and the periphery, via the spinal cord. Additional functions are ascribed to the cranial nerve nuclei, the reticular activating system and cardiorespiratory centres.
The cranial nerve nuclei within the brainstem are: I, III, IV in the midbrain; V, VI, VII, VIII in the pons; and IX, X, XI (cranial root) and XII in the medulla. There are additional multiple pathways which connect and co-ordinate these nuclei to produce complex reflexes such as the oculogyric reflex and control functions (swallowing, mastication, speech). Autonomic fibres are also carried in the brainstem with certain cranial nerves, principally III, VII, IX and X. The pontine reticular nuclei are critical to cortical arousal and conscious awareness. Neuronal destruction in this area is the basis of the principle of permanent unconsciousness inherent in the concept of brainstem death.

The brainstem also contains ill-defined ‘vital centres’ in the medullary and lower pontine reticular formation, under some control from the hypothalamus, which are essential for the maintenance and control of respiratory and cardiovascular function, again a critical component of brainstem death.

**Pathophysiology of brain injury**

**Vulnerability to injury**

The brain is susceptible to permanent damage for a number of reasons – key factors being high oxygen demand, deleterious impact of swelling within a fixed volume, specific anatomical considerations and the inability of neuronal tissues to undergo repair. The cerebral metabolic rate for oxygen (3.5 ml 100 g\(^{-1}\) min\(^{-1}\)) accounts for around 20% of the total resting oxygen consumption of the body, with cerebral blood flow (CBF) comprising almost 15% of the cardiac output (750 ml min\(^{-1}\)). There is little reserve, therefore, for hypoxia or ischaemia and unconsciousness occurs within 10 sec of interruption of the cerebral blood supply. Susceptibility to hypoxic injury is not uniform throughout the brain, the cerebral cortex being most vulnerable, followed by the forebrain nuclei. The cardiorespiratory centres within the brainstem are relatively resistant to hypoxic injury; this explains the persistent vegetative state (PVS) as an end product of severe injury characterised by cortical death and lack of awareness but intact ventilatory drive.

Although the primary purpose of the skull is to protect the underlying brain, once injury has occurred, the constraints of a rigid container on brain swelling cause an increase in intracranial pressure (ICP), thereby compromising cerebral oxygen delivery. The subsequent ischaemia further contributes to brain oedema triggering a progressive spiral of rising pressure and aggravated ischaemia. The ultimate effect of a globally high ICP is death of the brainstem due to coning (i.e. downwards extrusion through the foramen magnum). The internal contours of the skull and dural reflections can also lead to brainstem death by other mechanisms. Expanding lesions in either the temporal or parietal lobes lead to medial herniation of the uncus around the tentorium cerebelli causing compression and ischaemia of vital centres within the brainstem. The situation is compounded by the lack of capacity for primary neuronal repair. With no treatment options to reverse primary injury, management is restricted to prevention of secondary insults.

**Mechanisms of brainstem injury**

The most frequently seen pathologies associated with brainstem death are trauma, subarachnoid haemorrhage, hypoxia and meningitis. The viability of the brainstem may be compromised as part of a severe global insult (e.g. profound hypoxia, circulatory arrest or protracted hypotension beyond the limits of cerebral auto-regulation) or by more focal mechanisms (see Table 1).

**Markers of severity of brain injury**

The severity of brain injury can be assessed clinically, radiologically or by the use of neurospecific monitoring. Clinical assessment includes pupillary reactions, detection of localising signs and scoring systems such as the Glasgow Coma Score (GCS). Although the GCS is a reproducible tool for monitoring progress or deterioration, it does not differentiate between significant primary pathology and reversible causes such as the presence of depressant drugs, profound hypotension, hypothermia or a post-ictal state.

The primary role of radiological assessment of brain injury is in excluding a focal lesion amenable to surgical intervention. The early CT appearances of a severe diffuse axonal injury may be essentially normal and of no prognostic value. The later changes of effacement of the lateral ventricles, loss of the basal cisterns and a lack of differentiation between grey

---

**Table 1** Focal mechanisms compromising brainstem viability

<table>
<thead>
<tr>
<th>Direct insult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shearing injury of trauma or hanging</td>
</tr>
<tr>
<td>Focal ischaemia of vertebral/basilar artery pathology (e.g. traumatic vertebral dissection or in association with subarachnoid haemorrhage)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indirect insult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal pathology (e.g. posterior fossa or extradural haematoma)</td>
</tr>
<tr>
<td>Any global increase in ICP (e.g. trauma, hypoxia, hydrocephalus, infection, and hepatic encephalopathy, with secondary uncal herniation and eventual coning)</td>
</tr>
</tbody>
</table>
Brainstem death

and white matter in severe intracranial hypertension, complement the other markers of severe, potentially unsurvivable injury.

Neurospecific monitoring includes measurement of ICP, jugular bulb oximetry, processed EEG, transcranial Doppler (TCD) and multimodality intraparenchymal sensors. Information from these systems is used to direct treatment of ICP and manage discrepancies between oxygen delivery and consumption. If the deviations from normal values are extreme, multiple, or not responding to all currently available treatment strategies, these observations will have prognostic value.

Features of severe brain injury and brainstem death

In addition to a reduced level of consciousness, severe brain injury may be associated with localising signs and disturbance of both homeostasis and autonomic function. Cranial nerve lesions are dependent on the site of injury: anterior fossa (I–VI); middle fossa (VII, VIII); posterior fossa (IX, X). False localising signs such as VI nerve palsy may occur as the nerve is stretched. Pupillary constriction followed by dilatation is caused by stretching of III over the tentorium cerebelli by an expanding ipsilateral lesion, usually with herniation of the uncus.

Rising ICP leads to progressive compression of the brainstem with signs of both local pressure and indirect ischaemia. Cardiovascular changes occur as the cardiorespiratory centres are affected. The classic Cushing’s reflex of systemic hypertension and compensatory bradycardia may be observed but there may be tachycardia or other dysrrhythmias. The default status of the cardiovascular system after established brainstem death is usually one of hypotension and tachycardia. Diabetes insipidus (profound water loss, hypovolaemia and hypernatraemia) is a late sign of severe injury, occurring once the hypothalamic-pituitary axis is compromised. Control of temperature homeostasis may also be lost, the usual trend being towards hypothermia.

Definitions and diagnosis of brainstem death

There is no universally accepted definition of what constitutes death within either medicine or law and unlike the US, with their Uniform Determination of Death Act, death is not statutorily defined within the UK. However, the courts in England and Wales have adopted the ‘brain death criteria’ proposed by the Conference of Royal Colleges in 1976 and 1979, that death be regarded as ‘irreversible loss of the capacity for consciousness, combined with irreversible loss of the capacity to breathe’. On this basis, brainstem death is considered to equate with generic death of the individual.

Brainstem death testing is subject to strict controls and is regulated in the UK by Department of Health guidelines. Clinical testing alone by two experienced senior doctors is sufficient for the diagnosis. In other countries, confirmatory testing such as four vessel cerebral angiography, TCD and radioisotope scanning, designed to demonstrate absence of CBF, are required. In certain states in the US, a formal EEG is required to prove absence of cortical activity. In the UK, confirmatory techniques have been used occasionally when clinical testing has not been possible (e.g. when hypoxia precludes apnoea testing, local cranial nerve injuries, presence of long acting anaesthetic agents). In most scenarios without any of these confounding factors, confirmatory tests have not been shown to increase the accuracy of the clinical diagnosis of brainstem death.

The process of brainstem death testing

Preconditions

Brainstem death tests should be carried out by two medical practitioners holding full General Medical Council registration for more than 5 years, one of whom should be a consultant. They should be competent to undertake the tests, experienced in interpreting the results and independent of the transplant team. The doctors may carry out the tests separately or together but two sets of tests should always be performed to reduce the risk of observer error. There is no statutory interval that must elapse between the tests but this should be sufficient to reassure all those involved, including relatives and staff. For documentation purposes, the legal time of death is when the first set of tests confirms brainstem death, not when cardiac activity ceases.

Before a diagnosis of brainstem death can be made, various preconditions must be met:

(i) The pathology for the irreversible brain damage must be identifiable.

(ii) The patient must be unresponsive. There must be no consideration that this is due to sedative drugs, hypothermia (< 35°C), or potentially reversible circulatory, metabolic or endocrine disturbances. It is accepted that deviations from normal values may occur and the diagnosis is not precluded if these disturbances are a consequence of, rather than the cause of, neurological dysfunction.

(iii) The patient must be apnoeic, requiring mechanical ventilation. The possibility of neuromuscular blockade must be
excluded by means of a peripheral nerve stimulator or by eliciting deep tendon reflexes. Effects of narcotic or hypnotic drugs must also be excluded as a cause of ventilatory failure.

**Brainstem testing**

Brainstem death tests are designed to test function of cranial nerve nuclei and vital centres in the brainstem. Documentation of all test results should be on the appropriate template approved by the UK Department of Health. The features of brainstem death are as follows:

(i) The pupils are fixed with no direct or consensual response to light (tests II, III and parasympathetic outflow). It is not essential that the pupils be maximally dilated or equal in size and shape.

(ii) There is no corneal reflex on stimulation, conventionally elicited with cotton wool to avoid abrasion (tests V and VII).

(iii) There should be no motor response within the cranial nerve distribution in response to marked mechanical stimulation of any somatic area (tests V and VII). There should be no limb response to supra-orbital pressure (movements of limbs and trunk may occur due to spinal reflexes after brainstem death which, if not explained, may prove distressing to both relatives and staff).

(iv) The vestibulo-ocular reflexes should be absent on caloric testing (tests VIII and III). The tympanic membrane should first be visualised and any wax or debris removed as necessary. The head is flexed to 30° for this test and at least 50 ml of ice-cold water is instilled over one minute deep into each external auditory meatus. The eyelids are held open to observe any eye movements, principally nystagmus, during or after the instillation of water. If the performance of these tests on one side is impossible because of local injury or disease, the tests are not invalidated.

(v) There should be no gag reflex (contraction of the soft palate and oropharynx) when the posterior pharyngeal wall is stimulated with a spatula (tests IX).

(vi) There should be no cough or other reflex response to passage of a suction catheter down the endotracheal tube and stimulation of the carina (tests X).

**Apnoea testing**

No respiratory movements should occur when the patient is disconnected from the ventilator, with chest and abdomen exposed and directly observed. The patient should be pre-oxygenated and the P<sub>aCO</sub>₂ allowed to rise to 5.0 kPa prior to disconnection from the ventilator. Hypoxia should be prevented by oxygen insufflation through a catheter within the endotracheal tube. Sufficient time should be allowed for the P<sub>aCO</sub>₂ to rise to 6.65 kPa to exceed the normal threshold for stimulation of respiration, confirmed by measurement of arterial blood gases.

**Problems**

Different underlying pathologies can create uncertainty as to the appropriate timing of testing, with the guidelines recommending delay in cases of hypoxic brain injury. The evidence-base behind this approach is not robust, leaving practitioners in a dilemma as to when clinical judgement can determine whether brain injury should be considered irreversible.

Problems may also arise in establishing the diagnosis of patients who have been treated with sedative drugs for a prolonged period. The nature, number and dosage of sedative agents used in the neurological setting are often of higher magnitude than seen in other ICU patients and, in common with other critically ill patients, the metabolism and excretion of drugs is variable and often prolonged. Clinical judgement is often the only means of deciding when sedative agents can be excluded as a cause of unresponsiveness, or when it would be appropriate to administer specific reversal agents. For certain drugs such as thiopental (prolonged half-life, no antagonist), an argument can be raised for the use of confirmatory testing. Since drug measurement of blood concentrations are only available at certain centres, they are time-consuming and there is uncertainty about the concentrations that could cause or contribute to the state of unresponsiveness.

Problems also arise with interpretation of deviation from normal values of body temperature and biochemical variables. No specific levels are set within the guidelines, leaving a degree of uncertainty as to when either absolute levels or derangements across multiple fields would invalidate the diagnosis.

**Care of patients and relatives**

Communication with relatives is particularly important in such distressing circumstances. By ensuring they receive information in a sympathetic manner, medical and nursing staff can help relatives understand the reasons for and components of brainstem testing, and subsequent care plans. Although there is no template applicable to every family unit, any interval after the first set of tests can be used to introduce
the subject of organ donation. Regardless of the timing of request, relatives need time to consider and discuss these matters.

Care of the brainstem dead patient is subsequently dictated by the presence and wishes of the next of kin and the potential for donation. If donation is not an option, ventilatory support can be withdrawn at a time acceptable to all parties. If donation is considered, the aim of management is the maintenance of normal parameters to ensure optimal organ viability. This involves continued ventilation and cardiovascular support, and maintenance of fluid and electrolyte balance, acid-base status, and near normothermia. More specific interventions include replacement of hormones, including DDAVP, tri-iodothyronine and corticosteroids.

**Ethical and legal issues**

Brainstem death, as a by-product of medical technology, entered the literature before advances in surgical technique and immunosuppressive regimens made transplantation a viable longer term solution for organ insufficiency. It appears to be universally accepted that brainstem death is irreversible and confirms the futility of on-going active support. The later assertions that brainstem death be considered equivalent to generic death did not receive such widespread endorsement. The deliberations in Harvard and the UK were conceptual leaps, it being held first that permanent functional death of the brainstem constitutes brain death, and second that brain death could be equated with death itself. Certain premises as to the absoluteness of the condition were based on the inevitability of conventional death within a short time frame despite ventilatory support, an assumption not considered robust today.

The further contention that the death of the brainstem is inevitably associated with the loss of sensory awareness has also been challenged, on the basis that no monitoring modality can objectively demonstrate this. This has triggered debate on the advisability of general anaesthesia for organ retrieval. Since there was no necessity to define a patient as dead before supportive care could be discontinued on the grounds of futility, it appears that the principal advantage was the accommodation of organ retrieval at maximum viability, that is from the beating heart ‘cadaver’ donor. This apparent inter-linkage between new definitions of death and organ donation has ensured persistent controversy.

**Key references**

Anon. A definition of irreversible coma. Report of the ad hoc Committee of the Harvard Medical School to examine the definition of brain death *JAMA* 1968; 205: 337


See multiple choice questions 113–116.