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24.5.6 Brainstem death and prolonged disorders of consciousness Ari Ercole, Peter J. Hutchinson, and John D. Pickard

ESSENTIALS Advances in resuscitation and the advent of modern intensive care techniques to support the circulation challenge the simple definition of death in terms of loss of spontaneous circulation ('cardiac death'). Instead, death is now better regarded as an irreversible loss of the capacity for consciousness combined with irreversible loss of the capacity to breathe. Since the brainstem is required for both consciousness and spontaneous breathing, irreversible loss of brainstem function (e.g. after trauma, haemorrhage, or hypoxia/ischaemia) defines the state of 'brainstem death'. Clinical criteria for the diagnosis of brainstem death have been

published, but practice varies around the world. Several prolonged disorders of consciousness from coma (loss of wakefulness and awareness) through the vegetative state (wakefulness without awareness) to the minimally conscious state (wakefulness with some awareness) are now recognized. Brainstem death lies at the extreme end of this spectrum and is, by definition, permanent. Once potentially confounding conditions have been excluded, the secure diagnosis of vegetative state and minimally conscious state are based on expert, multidisciplinary observation that must take place over an extended period before permanence can be declared with sufficient certainty. Unlike those with brainstem death, patients with prolonged disorders of consciousness may survive for many years without physiological support. The care of such patients has huge social, societal, ethical, and economic implications. Introduction Advances in resuscitation and advanced physiological support make a robust definition of death more complicated than simply the absence of a spontaneous circulation. Instead, we must recognize death in terms of the irreversible loss of those functions that we consider essential for human existence. Consciousness is clearly a key aspect of human essence. But prolonged or permanent loss of capacity for consciousness forms part of a continuum. Patients in a vegetative state show no evidence of awareness and this state may be permanent. However, these patients may display clear wakefulness and spontaneous behaviours and this may continue without advanced physiological support, essentially indefinitely. Thus, a self-consistent definition of death must be a stronger statement: The irreversible loss of the capacity for consciousness combined with the irreversible loss of the capacity to breathe. Brain death and brainstem death Since the brainstem is essential for consciousness and breathing, the irreversible cessation of brainstem function ('brainstem death'), whether caused by a primary intracranial catastrophe (e.g. trauma, intracranial haemorrhage) or the result of extracranial cranial events (e.g. hypoxia or cardiac arrest), is the same as death of the patient. Despite advances in prehospital, accident and emergency, and intensive care management of neurological conditions, including cerebral trauma, haemorrhage, hypoxia and infarction, there remain many who succumb. The mechanism of death from these conditions may be sudden with cardiorespiratory decompensation and circulatory arrest, or the heart may continue to beat with respiration maintained by artificial ventilation but in the context of irreversible loss of brain function—the state of 'brain death'. It is important to distinguish between the definitions of brain death and brainstem death. The original term 'brain death' (US Harvard criteria 1968) implied complete death of the whole nervous system (flat electroencephalogram or EEG). This state is consistent with the notion of irreversibility, but islands of electrical activity may persist in the cortex and/or spinal reflexes may persist. Irreversible loss of brainstem function results in failure of neural transmission caudally to maintain respiration and cranially to maintain activation of the cerebrum by the reticular activating system. Thus, death of the brainstem is the same as death of the patient. In the United Kingdom, the term 'brainstem death' (death resulting from irreversible cessation of brainstem function) is preferred and legally recognized. In practice, many brainstem dead patients will also be brain dead. Criteria for diagnosis and brainstem death testing Worldwide practice varies, however in the United Kingdom specific criteria for the diagnosis of brainstem death have been published ('A code of practice for the diagnosis and confirmation of death'— see 'Further reading'). Confirmation of brainstem death is made by formal brainstem death testing. This follows strict protocols comprising several stages. Clinical prerequisites There should be no doubt that the patient's condition is due to irremediable brain damage of known aetiology. This may be obvious with computed tomography (CT) confirmation of a severe head injury or spontaneous haemorrhage, but may be much more difficult to establish (e.g. after cardiac arrest with an indefinite period of

24.5.6 Brainstem death and prolonged disorders of consciousness 5909 hypoxia). Continued observation and investigation may occasionally be required. The patient must be unconscious. Reversible causes such as primary hypothermia and potentially reversible circulatory, metabolic, or endocrine causes must be excluded. Electrolyte disturbances, and disorders of sodium homeostasis in particular, are common after devastating neurological injury and must be excluded as a primary cause of unconsciousness and corrected as appropriate. A sufficient period of time must be allowed for the elimination of any hypnotic or narcotic drugs. Barbiturates such as thiopentone (used in the management of intractable intracranial hypertension) present a particular difficulty due to their zero-order kinetics and consequent slow elimination after prolonged infusion as well as causing mydriasis, which interferes with clinical assessment. Laboratory drug assays may be helpful if there is doubt. The patient will be maintained on a ventilator because spontaneous respiration has ceased. The effects of neuromuscular blocking drugs and other respiratory depressants must be excluded. Confirmation with a nerve stimulator is advisable. High spinal cord injury must similarly be recognized as a potential confounder. Reasonable physiological control must be maintained throughout the tests and this can on occasion be difficult. It may not be ethically appropriate to institute escalating invasive support in an otherwise moribund patient simply to facilitate brainstem testing, particularly if this is likely to be delayed. Conduct of the tests

In the United Kingdom, the diagnosis of brainstem death should be made by at least two medically qualified practitioners who fulfil the following criteria:

- Both must have been registered with the General Medical Council for more than five years and be competent in the conduct and interpretation of brainstem testing.
- At least one must be a consultant. It is important that neither should have any perceived clinical conflict of interest (in particular, they must not be members of any transplant team).

Two complete sets of tests (see Box 24.5.6.1) must always be performed with both practitioners acting together. In the United Kingdom the second set of tests may immediately follow the first set at the discretion of the clinicians; there is no prescribed time that must elapse. Special considerations

Role of ancillary tests In the United Kingdom, radiological or neurophysiological studies do not form a routine part of the criteria unless clinical tests alone cannot be relied on (e.g. multiple facial and orbital fractures or a high spinal cord injury). Under such circumstances, ancillary tests such as including angiography, electroencephalography, or transcranial Doppler ultrasonography, may be carried out to reduce diagnostic uncertainty. However, such tests require specialist expertise and may not be universally available. False positives and negatives are both possible. CT angiography is increasingly available and promising as a technique that may be used to demonstrate absence of cerebral blood flow. However, the interpretation of such studies is not always straightforward (Fig. 24.5.6.1).

Children The concept of brainstem death is valid in children and infants older than 37 months' gestation; it should not be applied before this time. In older infants up to the age of two months, a diagnosis of death by neurological criteria is possible but may be difficult. In post-asphyxia or post-resuscitation patients, a period of at least 24 hours observation should be allowed as a precaution before testing as the possibility of residual sedative effects is greater. Furthermore, the respiratory system may be immature and a stronger hypercarbic stimulus is warranted in order to confidently determine irreversible apnoea. After the age of two months, testing may proceed in a similar manner as in adults.

Action following brainstem death testing Brainstem death is confirmed after both sets of tests have been completed with no evidence of reaction being found. The legal time of death is the time of completion of the first set of tests. Following confirmation of brainstem death, mechanical ventilation, and life support should be withdrawn. Depending on the known wishes of the patient, organ donation after brainstem death may be possible and this should be discussed

with the next of kin. It is important to avoid unnecessary delay in either discontinuing physiological support or undertaking organ retrieval after completion of the second set of tests on grounds of patient dignity. Expedient retrieval of organs maintains their function, so it is important when it is recognized that a patient is a potential organ donor.

Box 24.5.6.1 Tests for the diagnosis of brainstem death in the United Kingdom

- 1 The pupils are fixed and are unreactive to sharp changes in incident light intensity.
- 2 Absent corneal reflexes.
- 3 Absent oculo-vestibular reflexes on caloric testing.
 - With the head at 30 degrees to the horizontal plane, at least 50 ml of ice-cold water is injected into each external auditory meatus in turn over one minute while the eyes are examined for movement.
 - Patency of the external meatuses should first be confirmed by visualizing the tympanic membranes with an auroscope.
- 4 No motor response in the cranial nerve distribution in response to stimulation of any somatic area.
 - Spinal reflexes may occasionally be present in response to peripheral (but not central) stimulation but this does not invalidate the test.
- 5 Absent gag reflex to stimulation of the posterior pharynx.
- 6 Absent cough reflex in response to bronchial suctioning.
- 7 Absent respiratory effort.
 - The patient is preoxygenated with 100% oxygen.
 - Ventilation is adjusted so that a starting PaCO₂ is at least 6.0 kPa and the pH is less than 7.40 to ensure adequate respiratory drive. Higher targets may be required in patients with chronic CO₂ retention. Excessive hypercapnia/acidosis must be avoided however.
 - The patient is disconnected from the ventilator and 5 litre/min O₂ instilled by endotracheal catheter to maintain adequate arterial oxygen saturation.
 - The patient is observed for respiratory effort for five minutes after which it should be confirmed that the PaCO₂ has risen by more than 0.5 kPa.
 - Haemodynamic stability should be maintained throughout.

a Note that it may occasionally be impossible to test both sides due to unilateral disease. This does not invalidate these tests, but ancillary testing should be considered if neither side can be tested.

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5910 donor that the transplant coordinator is contacted as soon as possible and the stage that proceedings have reached is made clear. Careful counselling of family and friends is crucial throughout this process and they may or may not wish to be present for the testing process. Personal experience has shown that the specialist nurses in organ donation can provide strong and essential support to the relatives, irrespective of the decision of whether or not to donate.

Consciousness encompasses the state of wakefulness (where eyes are open and there is motor arousal) and awareness (the ability to experience external stimulus in some way). Acute loss of consciousness is a common consequence of severe brain injury from any aetiology. Such patients may transit through various states of unconsciousness during recovery. Sometimes such recovery may be very slow or incomplete, leaving patients with a prolonged disorder of consciousness. Prolonged disorder of consciousness encompasses a spectrum of disorders from 'coma' (where both wakefulness and awareness are absent), through the vegetative state (wakefulness without evidence of awareness) to the minimally conscious state (wakefulness with some awareness). Unlike brainstem death, vegetative state and minimally conscious state patients breathe spontaneously and are not ventilator dependent. Thus, such patients can survive for many years if adequately fed and nursed. States of prolonged disorder of consciousness are by definition long-term or permanent conditions with devastating impact on patients and their families as well as complex clinical, ethical, medicolegal, and socioeconomic ramifications. The vegetative and minimally conscious state

The term 'vegetative state' was introduced in 1972 by Jennett and Plum to describe the clinical condition resulting from loss of function in the cerebral cortex with a functioning brainstem (patients who are awake but not aware). Such patients have the capacity for

Fig. 24.5.6.1 CT

angiogram (a, b) of a patient with brainstem death after severe traumatic brain injury in whom extensive facial fractures prevented a full set of tests being carried out. Internal carotid arteries are opacified with contrast (a, arrows) but intracranial intravascular contrast is largely absent. Some opacification of the middle cerebral arteries (b, arrows) may nevertheless be seen due to pulsatile mixing of blood and this could be mistaken for blood flow demonstrating the need for caution in the interpretation of ancillary tests. However, a CT venogram (c) does not reveal contrast in the transverse or sigmoid sinuses (at black arrows) demonstrating complete absence of venous drainage.

24.5.6 Brainstem death and prolonged disorders of consciousness 5911 spontaneous or induced arousal, sleep-wake cycles, and spontaneous or reflexive behaviours. However, such patients fail to demonstrate evidence of awareness of themselves or their environment. By contrast, patients with minimally conscious state show reproducible (although variably inconsistent) responses to external stimulus or interaction with surroundings. The most common cause of prolonged disorder of consciousness after acute brain damage is severe head injury, the mechanism being severe diffuse axonal injury severing the subcortical connections over a wide area. Secondary hypoxic brain damage is a contributing factor in some traumatic cases. Most nontraumatic cases result from severe hypoxia-ischaemia of the brain after a cardiac arrest, near drowning, or strangulation, while a few result from severe hypoglycaemia in people with diabetes. Other causes are acute intracranial haemorrhage or infection. In adults the vegetative state can evolve gradually during the late stages of chronic dementing conditions and, in children, can result from severe congenital malformations of the brain or from progressive metabolic or chromosomal diseases affecting the brain. At post-mortem examination after acute hypoxic insults, there is commonly a widespread loss of cortical neurons. After acute traumatic and nontraumatic damage leading to vegetative survival, there is almost always severe bilateral thalamic damage, although the cortex may be relatively spared. There is also progressive degeneration over many months of neurons, nerve fibres, and their myelin sheaths remote from the site of initial damage, which is reflected during life in progressive enlargement of the ventricles as visualized by CT or MRI. Findings on the EEG are variable, but there is often loss of evoked cortical responses to somatic stimuli. Positron emission tomography in hypoxic cases shows severe depression of glucose metabolism in cortical grey matter, to levels found only in experimental deep barbiturate narcosis. Diagnosis Diagnosis has important implications for best-interest decision-making and end-of-life care. Unfortunately, there is no simple and reliable test for awareness and recovery may be very slow. As a result, the secure diagnosis of continuing vegetative state or continuing minimally conscious state necessarily involves observation by a multidisciplinary team of skilled observers over a prolonged period of at least four weeks. Furthermore, the confounding influence of medical instability must be ruled out, as must a diagnosis of widespread paralysis such as the locked-in syndrome, caused by brainstem damage which results in full awareness but leaving the patient able to communicate only by a yes/no code using the sole remaining motor power of blinking the eyelids or moving the eyes, which itself may be a hard to elicit and inconsistent finding due to fatigability. Diagnosis of vegetative state Patients may have long periods of spontaneous eye opening (hence the inappropriateness of calling this condition irreversible or prolonged coma). However, the eyes or head will never track a moving object. There may be a startle reaction to a sudden noise, but this is at best transient. All four limbs are paralysed and usually spastic, although spontaneous purposeless movements and orofacial movements, including unprovoked smiles and grimaces or tearing, may occur. Reflex posturing is seen and compatible with the diagnosis, as are generalized

arousal responses. Reflexive movements, such as facial grimacing or grasp reflexes, may be present. Groans may be heard but never words (rarely a single, inappropriate word may be generated, and this is thought to reflect small disconnected areas of cortical survival). There is no psychologically meaningful response to external stimuli, anticipatory or learned behaviour—no evidence of a working mind. It is concluded that, although awake, these patients are not aware and do not have any distress or pain. Misdiagnosis by nonexperts is common, and care is needed to exclude the minimally conscious state in which there are very limited responses to indicate some return of cognitive activity. Recent functional brain imaging and electrophysiological studies have revealed that a very few vegetative state patients can hear and understand before responses suggestive of minimally conscious state appear clinically. Diagnosis of minimally conscious state By contrast, patients with minimally conscious state may exhibit some awareness of themselves or external stimuli. Although reproducible, this will be inconsistent and may be very limited. Such responses may also be highly fatigable. Patients with minimally conscious state may be able to follow simple commands or issue yes/no responses, although these may not be accurate. There may be some verbalization or reaction to the linguistic content of verbal stimuli. Similarly, while smiling or crying is seen in patients with vegetative state, a minimally conscious state is distinguished by these behaviours being in reaction to the emotional content of stimuli. Prognosis It is not possible to make a diagnosis of a permanent disorder of consciousness with absolute certainty. Patients in a vegetative or minimally conscious state for some time can still make some recovery, however the likelihood diminishes over time. Of patients in a vegetative state one month after an acute insult, about half of head-injured individuals will regain some consciousness, but only a few of the nontraumatic cases do. The vegetative state may be declared to be permanent after six months for anoxic/ischaemic/infective/inflammatory or metabolic causes, but this diagnosis should not be made until at least one year after traumatic causes according to UK criteria. However, in all cases this needs to be individualized and a further 6–12 months of assessment may be needed if there is uncertainty. For minimally conscious state, emergence has rarely been documented after up to four years but is extremely unlikely after five years, and so a secure diagnosis of permanent minimally conscious state may take many years to establish. However, absolute time limits are not entirely helpful and need to be individualized. The severity of the initial injury, low levels of responsiveness, and limited clinical trajectory may all suggest that recovery is highly improbable. Most who recover consciousness remain very severely disabled and dependent, particularly if they have been in a vegetative state for several months. There is a high mortality in the first year but, once this period has been survived, patients can live for many years if tube feeding and good nursing care are maintained, and infective complications actively treated.

section 24 Neurological disorders 5912 Action after permanence is declared In England and Wales, the Mental Capacity Act 2005 sets out the framework for how decisions should be made on behalf of adults who cannot decide for themselves, and equivalent legislation exists in Scotland. Patients with prolonged disorders of consciousness do not have the mental capacity to make decisions about their care. Usually their premorbid wishes may not be explicitly known and it becomes necessary to determine what actions are in the patient's best interests, except in cases where some advance directive or appropriate lasting power of attorney exists. Those involved in caring for persons who lack capacity must act in their best interests and this extends to decisions surrounding the prolongation of that person's life. There is now a consensus in many countries that survival in a permanent vegetative state is of no benefit to the patient, and that it is therefore appropriate to withdraw life-sustaining treatment once permanence is declared. However, such decisions are not uncontroversial. Decisions regarding the withdrawal of life-sustaining treat-

ment in minimally conscious state is more contentious still due to the patient's degree of awareness of and interaction with the environment around them. Many courts in the United States of America and the United Kingdom have agreed that clinically assisted nutrition and hydration (CANH) is medical treatment that can be withdrawn if judged to be no longer in the best interests of the patient. Once this is done a peaceful death occurs in 8–12 days, and the cause of death is regarded as the original brain damage. Until 2017 in the United Kingdom it was a rule of practice to seek approval from the Court of Protection before withdrawing CANH. However, in more recent case law this was ruled to be unnecessary provided the clinicians have followed Good Clinical Practice and the case is otherwise uncontentious (i.e. provided that there is no dispute with family, other concerned parties, or among the treating team). This position brings the withdrawal of CANH for patients in a persistent vegetative state and minimally conscious state into line with the principles of withdrawing or withholding other life-sustaining therapies, and places the emphasis on acting in accordance with the patient's best interests— considering whether the outcome would have been acceptable to them and the likely decisions they would have made had they not lost their capacity. FURTHER READING Academy of Medical Royal Colleges (2008). A code of practice for the diagnosis and confirmation of death. AoMRC, London. Jennett B (2002). The vegetative state: medical facts, ethical and legal dilemmas. Cambridge University Press, Cambridge. Laureys S, Owen AM, Schiff ND (2004). Brain function in coma, vegetative state, and related disorders. *Lancet Neurol*, 3, 537–46. Monti MM, et al. (2010). Willful modulation of brain activity in disorders of unconsciousness. *N Eng J Med*, 362, 579–89. Royal College of Paediatrics and Child Health (2015). The diagnosis of death by neurological criteria in infants less than two months old. London, RCPCH. Royal College of Physicians (2013). Prolonged disorders of consciousness: national clinical guidelines. London, RCP. Wijdicks EF (2002). Brain death worldwide: accepted fact but no consensus in diagnostic criteria. *Neurology*, 58, 20–5.

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