Brainstem death and prolonged disorders of consciousness

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Abstract

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 (for example after trauma, haemorrhage or hypoxia/ischaemia) defines the state of 'brainstem death'. Clinical criteria for the diagnosis of brainstem death have been published, although practice varies around the world. Brainstem death lies at the extreme end of a spectrum of disorders of consciousness and is, by definition, permanent. A number of prolonged disorders of consciousness (PDOC) from coma (loss of wakefullness and awareness) through the vegetative state (VS; wakefulness without awareness) to the minimally conscious state (MCS; wakefullness with some awareness) are now recognised. Once potentially confounding conditions have been excluded, the secure diagnosis of VS and MCS is based on expert, multi-disciplinary observation and this must take place over an extended period before permanence can be declared with sufficient certainty. Unlike brainstem death, patients with PDOC may survive for many years without physiological support. The care of such patients has huge social, societal, ethical, and economic implications.

1 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 recognise 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.*

2 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 as may spinal reflexes. Irreversible loss of brainstem function results in failure of neural transmission both caudally to maintain respiration as well as cranially to maintain activation of the cerebrum by the reticular activating system. In this sense, 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 recognised. In practice, many brainstem dead patients will also be brain dead.

2.1 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 a number of stages.

2.1.1 Clinical prerequisites

There should be no doubt that the patients condition is due to irremediable brain damage of known aetiology. This may be obvious with CT confirmation of severe brain trauma or catastrophic spontaneous haemorrhage, but may be much more difficult to establish, e.g. after cardiac arrest with an indefinite period of hypoxia. Continued observation and investigation may occasionally be required. The patient must by definition 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 by 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 recognised 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.

2.1.2 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 5 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) 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 first elapse.

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 50ml of ice-cold water is injected into each external auditory meatus in turn over 1 minute whilst the eyes are examined for movement.
    - Patency of the external meatuses should first be confirmed by visualising 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 be 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 pre-oxygenated with 100% oxygen.
    - Ventilation is adjusted so that a starting $PaCO_2$ is at least 6.0kPa and the pH is less than 7.40 to ensure adequate respiratory drive. Higher targets may be required in patients with chronic CO_2 retention. Excessive hypercapnia / acidosis must be avoided however.
    - The patient is disconnected from the ventilator and 5L/min O_2 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 $PaCO_2$ has risen by more than 0.5kPa.
    - Haemodynamic stability should be maintained throughout.

* 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.

Box 1. Tests for the diagnosis of brainstem death in the United Kingdom.

2.2 Special considerations

2.2.1 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 including angiography, electroencephalography or transcranial Doppler ultrasonography, may be carried out to reduce diagnostic uncertainty. However such tests may not be universally available and require specialist expertise. False positives and negatives are both possible. CT-angiography in 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 (Figure 1).

2.2.2 Children

The concept of brainstem death is valid in children and infants older than 37 months gestation but 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 of 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.

2.3 Action following brainstem death testing

Brainstem death is confirmed after both sets of test have been completed with no evidence of reaction being found. The legal time of death is then the time of completion of the first set of tests. Following conformation 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. Expeditious retrieval of organs maintains their function, so it is important when it is a recognized that a patient is a potential organ 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.

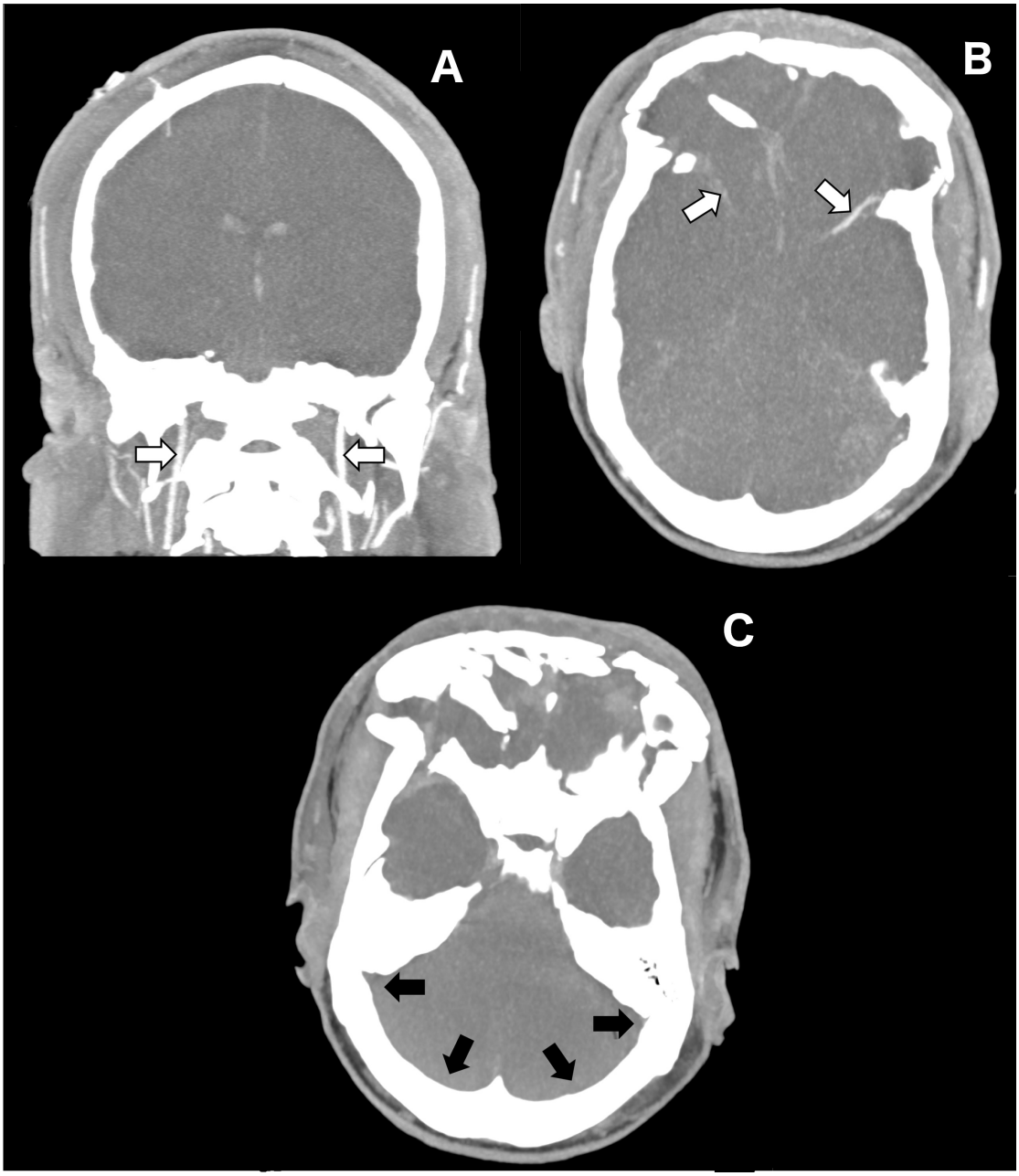

Figure 1: CT- angiogram (A, B) of patient with brainstem death after severe traumatic brain injury in whom extensive facial fractures prevented a full set of tests being carried out. Internal carotid arteries are opacified with contrast (A, arrows) but intracranial intravascular contrast is largely absent. 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.

3 Prolonged disorders of consciousness

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 (PDOC). PDOC encompasses a spectrum of disorders from 'coma' (where both wakefulness and awareness are absent), though the vegetative state (VS; wakefulness without evidence of awareness) to the minimally conscious state (MCS; wakefulness with some awareness).

Unlike brainstem death, VS and MCS patients breathe spontaneously and are not ventilator dependent. Thus such patients can survive for many years if adequately fed and nursed. PDOCs 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.

3.1 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 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 MCS show a reproducible (although variably inconsistent) response to external stimulus or interaction with surroundings.

The most common cause of PDOC 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 non-traumatic cases result from severe hypoxia/ischaemia of the brain after a cardiac arrest, near drowning, or strangulation, while a few result from severe hypoglycaemia. Other causes include acute intracranial haemorrhage and devastating infection or inflammation. 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 postmortem examination after acute hypoxic insults, there is commonly a widespread loss of cortical neurons. After acute traumatic and non-traumatic 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 may be 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 bar-

biturate narcosis.

3.2 Diagnosis

Diagnosis has important implications for best interests 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 VS or continuing MCS necessarily involves observation by a multidisciplinary team of skilled observers over a prolonged period of at least 4 weeks.

Furthermore the confounding influence of medical instability must be ruled out as must the a diagnosis of widespread paralysis such as the locked-in syndrome, caused by brainstem damage which results in full awareness but leaving the patient only able to communicate only by a yes/no code using the sole remaining motor power— blinking the eyelids or moving the eyes which itself may be a hard to elicit and inconsistent finding due to fatigability.

3.2.1 Diagnosis of VS

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, orofacial movements including unprovoked smiles and grimaces or tearing. Reflex posturing are seen and compatible with the diagnosis as are generalised 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 non-experts 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.

3.2.2 Diagnosis of MCS

By contrast, patients with MCS 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 MCS may be able to follow simple commands or issue yes/no responses although these may not be accurate. There may be some verbalisation or reaction to the linguistic content of verbal stimuli. Similarly, whilst smiling or crying is seen in patients with VS, MCS is distinguished by these behaviours being in reaction to the emotional content of stimuli.

3.3 Prognosis

It is not possible to make a diagnosis of permanent disorder of consciousness with absolute certainty. Patients in VS or MCS for some time can still make some recovery, however the likelihood diminishes over time. Of patients in the vegetative state one month after an acute insult, about half of head-injured individuals will regain some consciousness, but only a few of the non-traumatic cases do. The VS may be declared to be permanent after 6 months for anoxic/ischaemic/infective/inflammatory or metabolic causes but this diagnosis should not be made until at least 1 year after traumatic causes according to UK criteria. However in all cases this needs to be individualised and a further 6-12 months of assessment may be needed if there is uncertainty.

For MCS, emergence has rarely been documented after up to 4 years but extremely unlikely after 5 years and so a secure diagnosis of permanent MCS may take many years to establish. However absolute time limits are not entirely helpful and need to be individualised. 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 VS 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.

3.3.1 Action after permanence 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 in PDOC 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 patients best interests except in cases where some advance directive or an 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 VS 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 treatment in MCS is more contentious still due to the patients 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 to 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 amongst the treating team). Whilst at the time of writing this position is still potentially subject to legal challenge, it

brings the withdrawal of CANH for patients in PVS and MCS 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.

4 Further reading

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