Chapter 18
Brain Death

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The concept of brain death evolved when developments in critical care in the second half of the 20th century made it possible to sustain the cardiorespiratory functions of the body in the absence of brain function. In 1995, the American Academy of Neurology (AAN) published guidelines defining the medical standards for the determination of brain death and revised them in 2010. There is no published report of recovery of neurologic function after the diagnosis of brain death has been made according to these practice standards.

Brain death is defined as the complete and irreversible loss of all brain functions, including those of the brainstem. The mandatory diagnostic criteria for legal definition and declaration of brain death vary worldwide, even within different countries of the European Union or between States within the US, based on statutory tradition. Only very few countries do not accept brain death as a legal definition of death.

In adults, the most common causes of brain death are severe head injury and subarachnoid hemorrhage.

Clinical Examination

The gold standard for the determination of brain death is a series of neurologic tests, which may only be carried out if a number of prerequisites are met:

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Table 18.1 Clinical criteria for brainstem death

Coma	No motor response to painful stimuli (e.g., pressure on supraorbital nerve, painful stimulus to nail bed or sternum)
Absent brainstem reflexes	Pupils mid-size or dilated, no response to bright light
	No oculocephalic reflex (no grimacing nor eye opening with deep pressure on both condyles of the temporomandibular joint)
	No corneal reflex when wiping the cornea with cotton wool
	No oculovestibular response toward the side of the cold stimulus when ice water is injected into the external ear canal
	No cough reflex on bronchial suctioning
	No gag reflex on stimulation of the posterior pharynx
Apnea	No respiratory effort when patient is disconnected from the ventilator and CO_2 is allowed to at least 20 mmHg above baseline

- The cause of coma is known with a high degree of certainty and is demonstrably irreversible. That implies that the clinical or neuroimaging evidence of a central nervous system catastrophe is consistent with irreversible loss of brain function.
- Medical conditions that may confound clinical assessment, such as hypothermia, severe hypotension or severe electrolyte, acid-base and endocrine disturbances must be corrected.
- Drug intoxication, poisoning or neuromuscular blocking agents have to be ruled out.

The diagnosis of brain death is primarily clinical. No other tests are required if the full clinical examination including the brainstem reflexes and apnea test is conclusively performed.

The three cardinal findings in brain death are coma, absence of brainstem reflexes, and apnea (Table 18.1).

Confirmatory Tests

The role of confirmatory tests differs among countries but they generally are indicated when a specific part of the clinical examination cannot be performed or is deemed unreliable (Table 18.2).

In the United States, the choice of tests is left to the discretion of the physician. Confirmatory tests demonstrate either extinct brain function (electroencephalography, evoked potentials) or cessation of cerebral blood flow (cerebral angiography, radionuclide angiography, cerebral perfusion scintigraphy).

Cerebral Angiography

Four-vessel cerebral angiography has traditionally been the gold standard for documenting cessation of cerebral blood flow. The arterial circulatory arrest within the cranium develops in a distal-to-proximal direction as intracranial hypertension progresses. Thus, the level of contrast stop descends from the subarachnoid to the

Table 18.2 Conditions that may interfere with the clinical diagnosis of brain death and may require ancillary tests

Severe facial or cervical spine trauma confounding cranial nerve assessment
Preexisting pupillary abnormalities
Toxic levels of CNS-depressant drugs or neuromuscular blockage agents
Severe chronic pulmonary disease or obesity resulting in chronic retention of carbon dioxide

cervical levels (Fig. 18.1a–g). Cerebral angiography is conclusive if the flow in the posterior circulation ceases at the foramen magnum and at the petrosal portion of the carotid artery in the anterior circulation. The external carotid circulation generally is patent, and filling of the superior sagittal sinus may be delayed.

There have been a number of case reports about clinically brain-dead patients where angiography demonstrated persistent filling of intracerebral arteries. The phenomenon of persistent cerebral blood flow can be found when intracranial pressure has not exceeded cerebral perfusion pressure yet. The progressive deterioration of cerebral circulation until its complete arrest has been documented with serial angiography over a period of about 45 min. Isolated venous sinus visualization is not uncommon and occurs in up to 57 % of brain-dead patients. It represents trivial blood flow and confirms brain death. Persistent arterial flow does not exclude brain death, but the diagnosis should be confirmed either by means of repeated studies or other tests.

CT Angiography

Although conventional angiography remains the standard imaging method for cerebral circulatory arrest, CTA is emerging as an alternative. Conventional angiography is highly sensitive, but invasive, expensive and time-consuming. It exposes potential donor organs to toxic contrast material, and it requires an experienced neuroradiologist, potentially leading to delays. CTA confers a number of advantages such as lower invasiveness, wider availability and less operator dependence. It has been shown to have a sensitivity of 69.7–95 % compared with conventional angiography in a number of studies. However, a recent publication described residual contrast enhancement in pericallosal arteries and horizontal portions of the middle cerebral artery and/or the internal cerebral veins in up to 25 % of the clinically brain-dead patients. This mandates repetitive CTAs and increases the time window between clinical brain death and radiographic confirmation. Currently there is no international consensus about the use of CTA for the detection of cerebral circulatory arrest.

Transcranial Doppler Ultrasonography

The velocity waveform of the basal cerebral arteries changes in a characteristic way as circulatory arrest evolves. Four steps can be distinguished (Fig. 18.2a–c):

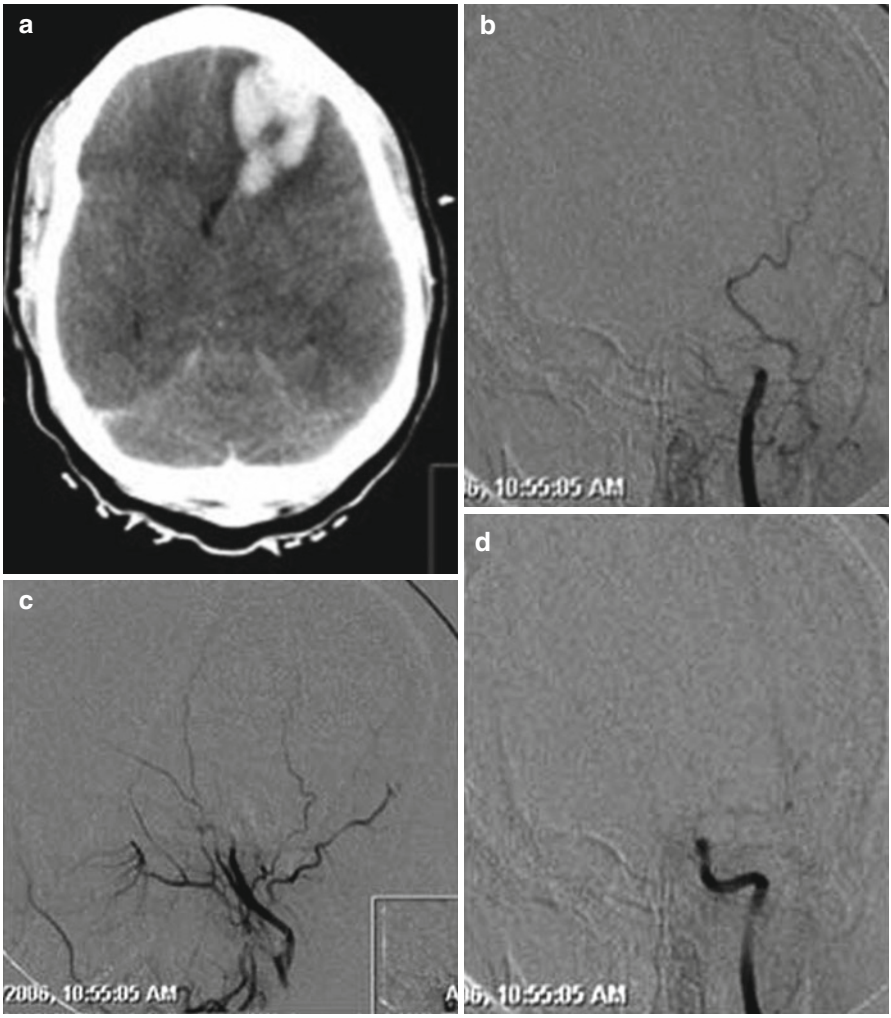

Fig. 18.1 Non-contrast computed tomography scan of the head (**a**) in an anonymous young female who was found comatose and tested positive for multiple drugs with evidence of a space-occupying left frontal lobar hemorrhage and diffuse brain edema. Cerebral angiography was pursued to rule out an underlying vascular anomaly. Left common carotid artery injection demonstrated cessation of flow distal to the supraclinoid segment of the left internal carotid artery in frontal (**b**, arterial phase; **d**, late capillary phase) and lateral plane (**c**, arterial phase; **e**, late capillary phase) leading to contrast stasis in the extradural segments of the left internal carotid artery. The left external carotid artery branches well opacified. Circulatory arrest at the foramen magnum was confirmed for the left vertebral artery (**f**, arterial phase; **g**, capillary phase) given the lack of opacification of any intradural segment of the left vertebral artery (Images courtesy of Darren B. Orbach, Interventional Neuroradiology, Boston Children's Hospital)

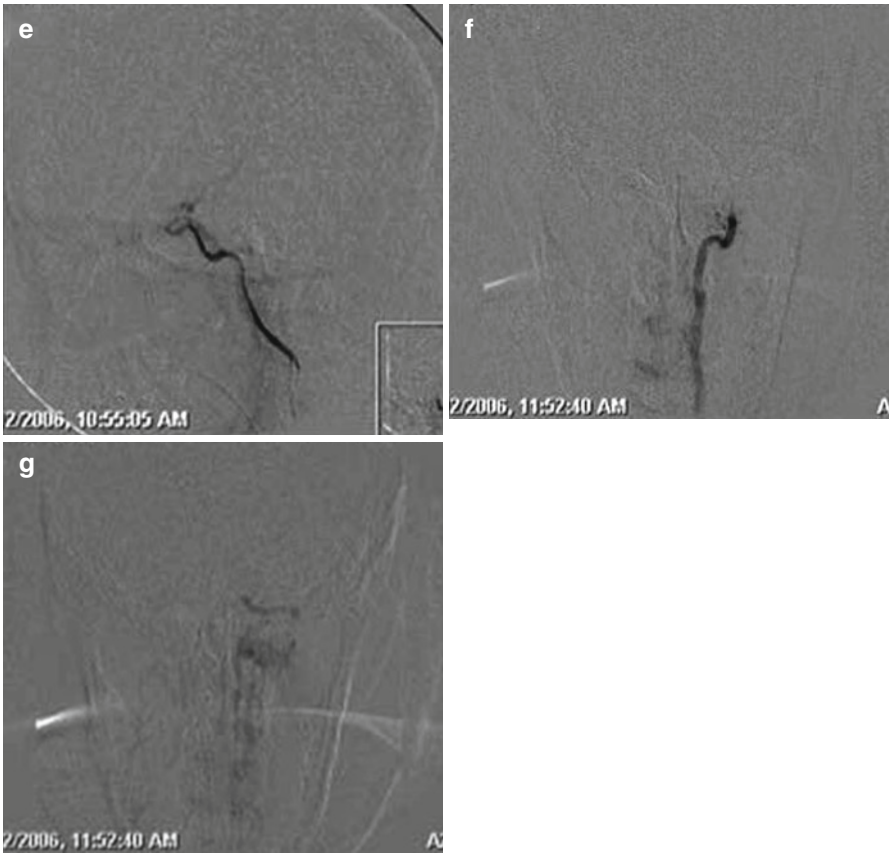

Fig. 18.1 (continued)

- Stage 1, *systolic peaks* – With increasing pulsatility, the flow velocity approaches zero at the end of diastole; therefore, only forward flow can be seen in systole.
- Stage 2, *oscillating flow* – Cerebral perfusion has ceased when forward and reverse flow is almost equal. This correlates with the angiographic appearance of cerebral circulatory arrest.
- Stages 3, *systolic spikes* – The hallmark of the third stage are *systolic spikes* as blood velocity decreases and intracranial pressure increases.
- Stage 4, *no signal* – No intracranial flow can be detected. This final stage mandates referencing with insonation of the extracranial internal carotid and vertebral arteries to rule out transmission problems.

Before using transcranial Doppler (TCD), the absence of brainstem reflexes should be ascertained as flow arrest in the middle cerebral arteries has been shown to precede the complete loss of brainstem function. The Task Force Group on

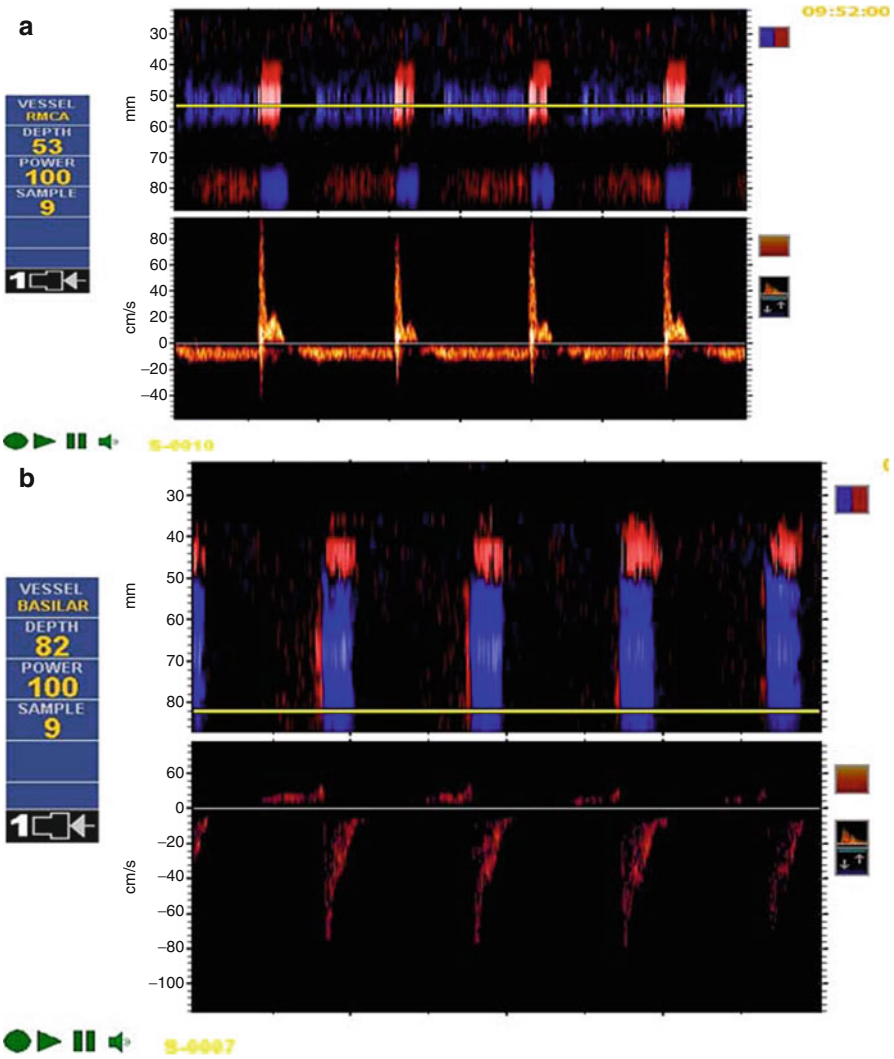

Fig. 18.2 A 54 year-old female patient with intracerebral hemorrhage from large right frontal AVM. Following staged embolization, the patient became unresponsive, hypotensive and progressed to deep coma with fixed and dilated pupils. Computed tomography of the head revealed rehemorrhage and contrast extravasation indicating a small perforation secondary to guide wire manipulation. The initial ICP readings were 40–50 mmHg despite the administration of mannitol, barbiturates and hypertonic saline. Doppler spectral wave forms and color M-mode display of the right middle cerebral artery (**a**) indicated antegrade flow in systole and retrograde flow in diastole or oscillating flow. TCD reading from the basilar artery (**b**) demonstrated oscillating flow. Recording of the left extracranial internal carotid artery (**c**) with spectrum analysis indicating systolic peaks (Images courtesy of Colleen Douville, Swedish Neuroscience Institute, Seattle)

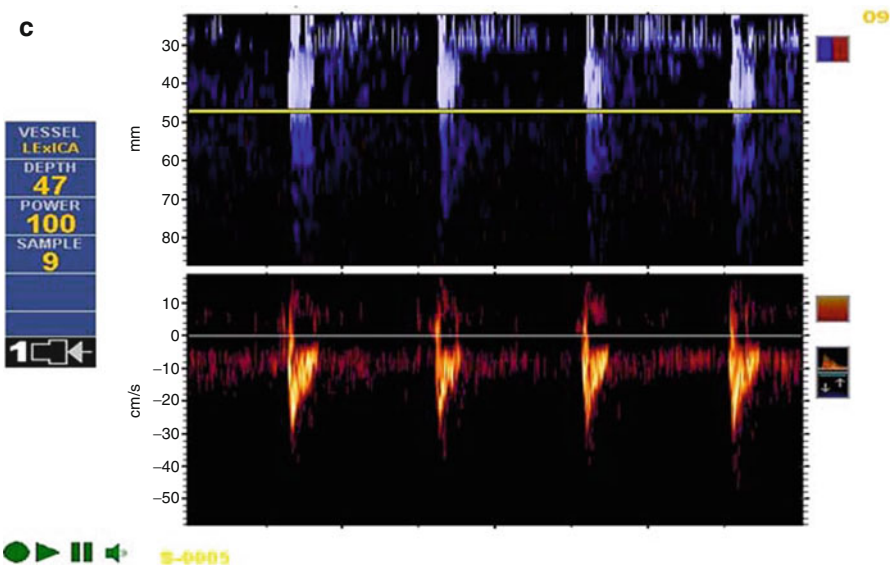

Fig. 18.2 (continued)

Cerebral Death of the Neurosonology Research Group of the World Federation of Neurology states that cerebral circulatory arrest can be confirmed if the extra- and intracranial Doppler findings have been documented bilaterally on two examinations at an interval of at least 30 min (Table 18.3).

The availability at the bedside and its non-invasive nature render TCD advantageous over cerebral angiogram as a confirmatory test. However, despite its high sensitivity of 95 % and specificity of 99 %, the widespread use of TCD is limited by its operator dependency and the fact that 5–10 % of patients cannot be examined because of the absence of a bone window or of no initial flow.

Nuclear Imaging

Radionuclide brain perfusion studies are costly, but correlate well with cerebral angiography. Delayed images are usually definitive for the presence or absence of cerebral blood flow. The advantages of cerebral perfusion scintigraphy are the direct visualization of perfusion of the cerebral cortex and brainstem, and hence brain viability because the radiopharmaceutical is taken up by grey and white matter in proportion to blood flow. It is tolerant of metabolic aberrations and pharmacologic intoxicants. The radiopharmaceuticals used in scintigraphy have no deleterious effects on potential donor organs. It is not affected by electrical interference, and the presence of skull defects does not preclude its use.

Table 18.3 Criteria allowing a the diagnosis of cerebral circulatory arrest by transcranial ultrasound

Oscillating flow with a net flow of 0 or systolic spikes found bilaterally in any cerebral artery
Systolic spikes <200 ms duration, peak systolic velocity <50 cm/s, no flow signal during the remaining cardiac cycle
The diagnosis established by the intracranial examination must be confirmed by the extracranial bilateral recording of the common carotid, internal carotid and vertebral artery. Complete absence of flow may not be reliable owing to inadequate transtemporal windows
Absence of a large craniectomy defect or ventriculostomy is mandatory as they interfere with the development of ICP

Radionuclide angiography is limited by being prone to technical failure as a result of inadequate bolus injection of the radiopharmaceutical when a non-brain binding agent such as diethylenetriaminepentaacetic acid (DTPA) labeled with ^{99m}Technetium is used. Brain-specific agents like ^{99m}Technetium-hexamethyl propyleneamine oxime (HMPAO) are advocated now because their interpretation is far less dependent on the quality of the bolus. Lack of visualization of the brain on delayed images could conceivably be caused by improper preparation or instability of the radiopharmaceutical. Flow images will help to confirm lack of brain blood flow when the brain is not visualized on delayed images using ^{99m}Tc-HMPAO. Radionuclide angiography carries an up to 25 % likelihood of showing persistent viable spots of brain tissue in clinically brain-dead patients.

Teaching Points

1. The diagnosis of brain death is primarily a clinical one.
2. Imaging can be indicated when the clinical tests are thought to be unreliable or it is impossible to carry them out.
3. Cerebral angiography is the gold standard. It is conclusive if the flow in the posterior circulation ceases at the foramen magnum and at the petrosal portion of the carotid artery in the anterior circulation.
4. CT angiography, transcranial Doppler or nuclear imaging offer alternatives but each have a number of limitations.