4 Brain Death Diagnosis

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I know when one is dead and when one lives.
She's dead as earth. Lend me a looking-glass.
If that her breath will mist or stain the stone,
Why then, she lives.

W. Shakespeare, King Lear, Act V, Scene III

During Shakespeare's time in the late sixteenth and early seventeenth century, not breathing and the absence of blood circulation were universal criteria to declare someone dead. For almost two centuries, doctors have been using the stethoscope to diagnose death. In the twentieth century, the discovery of cardiopulmonary resuscitation, defibrillation, and pharmacologic therapies to counteract heart arrest changed the definition; cardiac arrest could be established as a clinical death, giving rise to the possibility of post-arrest resuscitation. For almost 50 years, doctors have thus been diagnosing death by applying neurological criteria.

The brain is anatomically divided into the cerebrum, with its outer shell, the cortex; the cerebellum; and the brain stem, composed of the midbrain, the pons, and the medulla oblongata. Traditionally, the cerebrum has been considered the "higher brain" because it has primary control of consciousness, thought, memory, and feeling. The brain stem is the "lower brain," because it organizes spontaneous, vegetative functions such as swallowing, yawning, and sleep–wake cycles. At the same time, "higher brain" functions such as cognition or consciousness are not mediated strictly by the cerebral cortex, but they result from complex interactions between the brain stem and the cortex. Breathing is controlled in the brain stem, particularly the medulla. Neural impulses originating in the respiratory centers of the medulla stimulate the diaphragm and intercostal muscles, which cause lung inflation and deflation. Generally, respiratory centers adjust the rate of breathing to maintain the correct levels of carbon dioxide and oxygen. During heavy exercise, sighing, coughing, or sneezing, other areas of the brain regulate the activities of the respiratory centers or even briefly take direct control of respiration. The destruction of the brain's respiratory center stops respiration, thus causing a sudden loss of oxygen to the heart that causes it to cease functioning. Therefore, the traditional signs of life, respiration and heartbeat, disappear: the person is considered dead.

The irreversible loss of the capacity for consciousness combined with the irreversible loss of

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AUX CLINIQUES UNIVERSITAIRES DE LOUVAIN

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Contribution importante d'un jeune chercheur belge

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Les pigeons de la place Poelaert resteront-ils insaisissables ?

Bonn face

Pomme de discorde: la politique extérieure

Fig. 4.1 From the first page of "La Libre Belgique," August 10–11, 1963. "Two patients survive several weeks after transplantation of a kidney previously removed from a cadaver. Important contribution of a young Belgian investigator"

the capacity to breathe is acknowledged globally as death. Death is a result of the irreversible loss of both these functions in the brain [1]. Specifically a brain stem failure can originate from an intracranial lesion (trauma, hemorrhage, ischemia) or from an extracranial cause (cardio-respiratory arrest, cerebral anoxia). The idea of brain death arose in the 1950s when physicians began sustaining patients who lacked brain function by mechanical ventilation; these patients appeared "alive" based on regular heart rhythm and blood pressure. It was clear that the advent of mechanical ventilation halted the unavoidable circulatory breakdown that always follows respiratory arrest. Therefore, in those cases, it became necessary to diagnose death with neurological criteria. In 1959, Wertheimer et al. [2] described the "death of the nervous system." And in the same year, the French neurophysiologists Mollaret and Goulon [3] defined a state of coma in which the brain appeared irreparably damaged and ceased to function but in which the heart and lung function could be maintained artificially. They called this state "coma depassè." A few years before, in 1954, Joseph Murray, Nobel Laureate in 1990, performed the first human organ transplant by taking a kidney from an identical twin, and in 1962; he performed the first successful kidney transplant from a human cadaver [4]. One year later, Starzl et al. [5] performed the first liver transplant, and Hardy et al. [6] performed the first lung transplant. For all these transplants, donors were transferred into the operating room, and mechanical ventilation was stopped; organ retrieval could start only when the donor's heart stopped beating. At this time, donors were declared dead by classic cardiorespiratory criteria [7]. In 1963, Guy Alexandre, a Belgian surgeon at the Catholic University of Louvain, performed the first transplantation using a heart-beating, brain-dead donor (Fig. 4.1). Mechanical ventilation was not

Table 4.1 Dr. Alexandre's criteria for brain death diagnosis

Precondition: severe craniocerebral injury
Criteria for brain death diagnosis:
1. Complete bilateral mydriasis
2. Complete absence of reflexes, both natural and in response to profound pain
3. Complete absence of spontaneous respiration, 5 min after mechanical respiration has been stopped
4. Falling blood pressure, necessitating increasing amounts of vasopressor drugs (adrenaline) or Neo-Synephrine (phenylephrine hydrochloride)
If all conditions are met, observation is <6 h, and EEG must be flat

Table 4.2 Harvard criteria for brain death diagnosis

Precondition:	Irreversible cerebral damage
	Exclusion of two conditions: hypothermia (below 90 °F) and central nervous system depressants, such as barbiturates
Criteria:	Pupil fixed and dilated and will not respond to a direct source of bright light
	Non-receptivity and unresponsiveness to even the most intensely painful stimuli
	Ocular movement (to head turning and to irrigation of the ears with ice water) and blinking are absent
	No evidence of postural activity (decerebrate or other)
	Swallowing, yawning, vocalizations are absent
	Corneal and pharyngeal reflexes are absent
	Stretch of tendon reflexes cannot be elicited; plantar or noxious stimulation gives no response
	No movements or breathing
	Observations covering a period of at least 1 h by physicians are adequate to satisfy the criteria of no spontaneous muscular movements or spontaneous respiration [established by turning off the respirator for 3 min] or response to stimuli such as pain, touch, sound, or light
	All of the above tests shall be repeated at least 24 h later with no change
	Flat EEG

discontinued, and the team did not wait for the donor's heart to stop beating [8, 9].

The graft worked immediately after transplant, and serum creatinine levels were normal after a few days; however, the recipient died of sepsis on postoperative day 87 [8]. Dr. Alexandre's criteria for brain death criteria are shown in Table 4.1.

In 1966, Richard Lillehei and William Kelly et al. performed the first successful pancreas transplant [10, 11]. In 1967, Dr. Christiaan Barnard, in Cape Town, South Africa, performed the first heart transplant [12]. The surgical team brought a brain-dead donor into the operating room with the recipient; the mechanical ventilation was stopped, and everyone waited for the donor's heart to stop beating. Technically, the donor was not "brain dead" at the time of organ retrieval, but he was declared dead by classical cardiorespiratory criteria [13]. Even Barnard [12] stated, "As soon as the donor had been certified dead (when the electrocardiogram had not shown activity for 5 minutes and there was absence of any spontaneous respiratory movements and absent reflexes)… the donor chest was then opened rapidly."

The following year in the United States, due to organ transplantation's worldwide diffusion, the "Ad Hoc Committee of the Harvard Medical School" established criteria for brain death before organ retrieval [14]. In a comatose patient, the Commission defined brain death as a condition characterized by unresponsiveness, a lack of receptivity, and the absence of movements, breathing, and brain stem reflexes (Table 4.2).

Furthermore, the declaration of death should be performed by physicians that were not involved in transplantation procedures and would not participate in the process of transplantation.

Table 4.3 Declaration of Sydney

Determining the time of death is in most countries the legal responsibility of the physician and should remain so. Usually the physician will be able without special assistance to decide that a person is dead, employing the classical criteria known to all physicians. Two modern practices in medicine, however, have made it necessary to study the question of the time of death further: 1—the ability to maintain by artificial means the circulation of oxygenated blood through tissues of the body which may have been irreversibly injured, and 2—the use of cadaver organs such as heart or kidneys for transplantation. A complication is that death is a gradual process at the cellular level, and tissues vary in their ability to withstand oxygen deprivation. However, clinical interest lies not in the preservation of isolated cells but in the fate of a person. Here, the point of death for the different cells and organs is not as important as the certainty that the process has become irreversible by whatever techniques of resuscitation may be employed. This determination will be based on clinical judgment supplemented if necessary by a number of diagnostic aids, of which the electroencephalograph is currently the most helpful. However, no single technological criterion is entirely satisfactory in the present state of medicine, nor can any one technological procedure be substituted for the overall judgment of the physician. If transplantation of an organ is involved, the decision that death exists should be made by two or more physicians, and the physicians determining the moment of death should in no way be immediately concerned with the performance of transplantation. Determining the point of death of the person makes it ethically permissible to cease attempts at resuscitation and, in countries where the law permits, to remove organs from the cadaver provided that prevailing legal requirements of consent have been fulfilled.

The same day, on August 5, 1968, the 22nd World Medical Assembly, meeting in Sydney, Australia, announced the Declaration of Sydney [15] (Table 4.3). In this document, it was stated not only that "Death is a gradual process at the cellular level with tissues varying in their ability to withstand deprivation of oxygen" but also that death "lies not in the preservation of isolated cells but in the fate of a person."

4.1 Brain Stem Damage

In 1971, Mohandas and Chou [16] described lesions to the brain stem as a critical constituent in brain damage. This consideration was later confirmed by the Conference of Medical Royal Colleges and their Faculties in the United Kingdom [17], where brain death was stated as an overall irreversible loss of brain stem function. This announcement, made in 1981, allowed the subsequent conclusions and guidelines of the President's Commission for the Study of Ethical Problems in Medicine and Behavioral Research [18] that enacted the Uniform Determination Death Act [19] (UDDA): "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards." In other words, "death is a unitary phenomenon which can be accurately demonstrated either on the traditional grounds of irreversible cessation of heart and lung functions or on the basis of irreversible loss of all functions of the entire brain [18]." The UDDA defines that "for legal and medical purposes an individual who has sustained irreversible cessation of all functioning of the brain, including the brain stem, is dead."

Neurological criteria can indicate death by attesting the loss of the whole brain, including, but not limited to, the brain stem [20]. A subject may be artificially supported for respiration and circulation after all brain functions irreversibly cease, but physicians have developed techniques for diagnosing the loss of brain functions while cardiorespiratory support is given.

Once the brain is deprived of adequate stores of oxygen and glucose, its neurons will irreversibly lose any activity. In the adult, this deprivation for more than a few minutes causes some neuron loss [21]. Thus, even in the absence of direct trauma and edema, brain activity can be lost if its circulation is disrupted. If blood flow is discontinued, the nervous tissue damage is characterized by complete self-digestion (autolysis) patterns over the ensuing days. If the brain lacks all functions, consciousness is gone. Whereas some spinal reflexes often persist in such patients (because circulation to the spine is separate from that of the brain), all reflexes controlled by the brain stem, as well as cognitive, affective, and integrating functions are absent. Respiration and circulation in these bodies may be made by a mechanical ventilator together with massive medical management. In adults who had irreversible cessation of the functions of the entire brain, this artificial performance can last a short time, but the heart usually stops beating within 2–10 days. However, a small child who has lost all brain functions will have a cardiac arrest within several weeks [22].

A less severe injury to the brain can cause mild to profound damage to the cortex, lower cerebral structures, cerebellum, brain stem, or some combination thereof. The cerebrum, especially the cerebral cortex, is damaged first and more easily than the brain stem by the loss of blood flow; a 4–6 min loss of blood flow caused by a cardiac arrest will create permanent damage in the cerebral cortex, whereas the relatively more resistant brain stem may continue to function [21]. In this case, the main functions of the cerebrum are irrevocably lost, and the patient remains in a "persistent vegetative state" [23]; the patient may show spontaneous, involuntary movements such as yawns or facial grimaces, their eyes may be open, and they may be capable of breathing without assistance. However, lacking the superior cerebral function, any patient's movement does not mean that he is aware of himself or his environment. This was the case for Karen Ann Quinlan, for whom medical and nursing care, including feeding through intravenous or nasogastric tubes, and antibiotics for recurrent pulmonary infections allowed a survival longer than 10 years [24].

The cranial nerves, except I, II, and the spinal component of XI, originate in the brain stem, and the diagnosis of their functional loss confirms irreversible damage to this structure and by association to the reticular activating system and medulla oblongata. The following cranial nerve reflexes must be examined to diagnose their absence (Fig. 4.2).

- Pupils should be fixed in diameter and unresponsive to light (midposition with respect to dilation, 4–6 mm), absence of papillary reflex to light: cranial nerves II and III.
- When each ear is instilled with iced water, nystagmus or any eye movements are absent (vestibuloocular reflex): cranial nerves II, IV, VI, VIII.
- Absence of corneal reflex: cranial nerves V, VII.
- No facial or limb movement when supraorbital pressure is applied: cranial nerves V, VII.
- Oculocephalic reflex: eyes remain midline when the head is turned rapidly horizontally and vertically: afferent limbs labyrinth, vestibular nerve, neck proprioceptors, efferent limbs cranial nerves III and VI.
- Absence of response to painful stimuli on supraorbital pressure or deep pressure on both condyles of the temporomandibular joint: afferent limb V nerve, efferent limb VII nerve.
- Absence of coughing in response to tracheal suctioning and absence of gag reflex after stimulation of the posterior pharynx: cranial nerves IX and X.
- Apnea testing positive.

When all cranial nerve reflexes are absent, the apnea testing is performed to establish the clinical diagnosis of brain death.

In apnea testing, the patient is disconnected from the respirator, and a cannula, supplying pure oxygen at a rate of 4–10 l/min, is carried into the endotracheal tube down to the level of the carina. The cannula will ensure sufficient alveolar ventilation and the transport of oxygen to the blood in absence of respiratory movements. Before testing, preoxygenation with 100 % O_2 should be performed for at least 10 min to avoid hypoxia. Preoxygenation arterial PO_2 values should be ≥200 mmHg, which helps avoid possible hypocapnia that may be caused by hyperventilation or by high tidal volume settings on the mechanical ventilator. The corporeal temperature should be ≥32 °C, and it is important to ensure that the arterial PCO_2 or $PaCO_2$ is normal or greater than

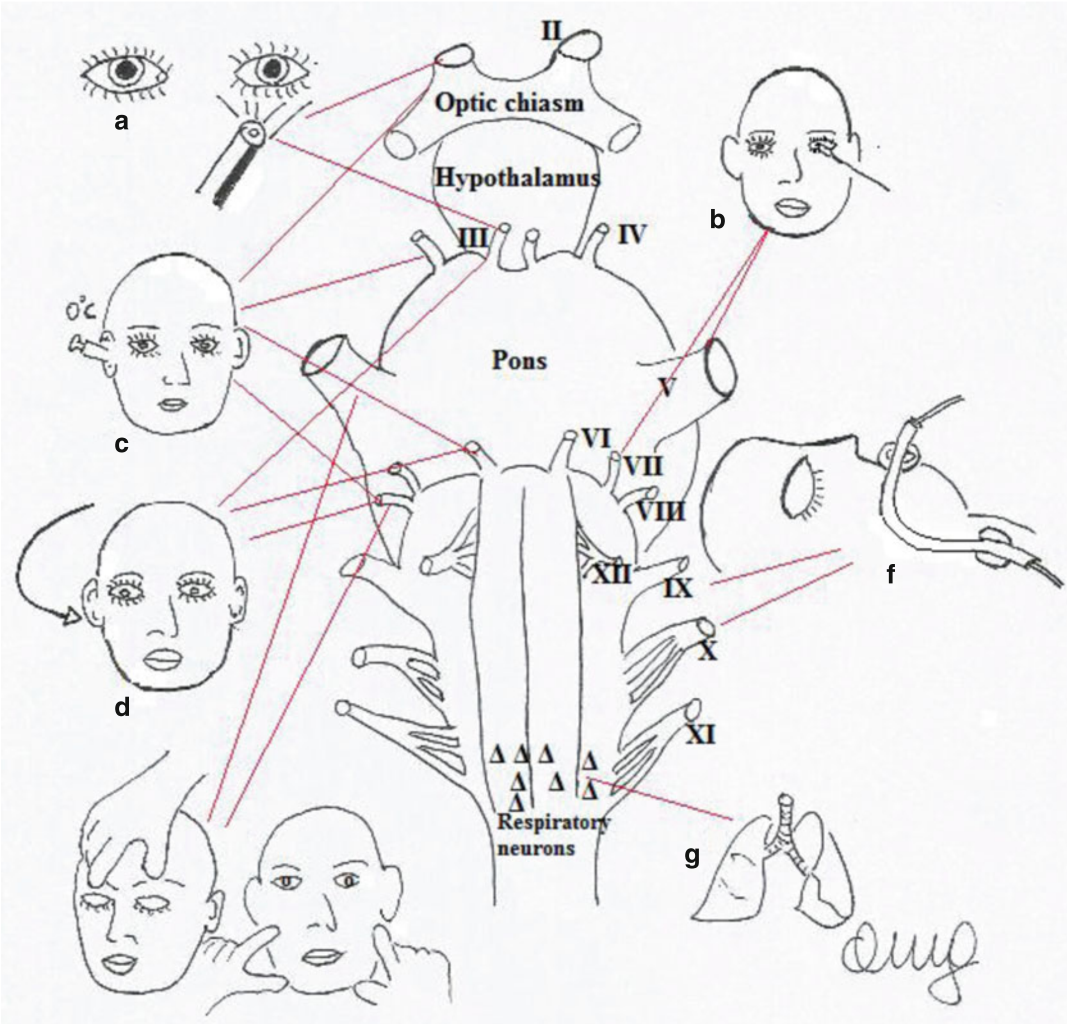

Fig. 4.2 Brain stem reflexes in brain death (**a**) Light reflex. (**b**) Corneal reflex. (**c**) Vestibuloocular reflex. (**d**) Oculocephalic reflex. (**e**) Absent response to pain stimuli. (**f**) Cough reflex. (**g**) No breathing

40 mmHg. A systolic blood pressure of at least 90 mmHg is recommended. Apnea testing is completed when no breathing effort is observed at a $PaCO_2$ of 60 mmHg or with a 20 mmHg increment from baseline; in this case, the test result is positive and confirms the diagnosis of brain death [25].

When the clinical examination establishes a diagnosis of brain death, it is fundamental to exclude the possibility of misdiagnosis, and confirmatory tests are recommended [26].

The misdiagnosis of brain death is possible in the following conditions: hypothermia, drug intoxication, and locked-in syndrome. In hypothermia, the brain stem reflexes are not present if the core temperature is <28 °C; these deficits can be reversible [27].

Many sedative and anesthetic drugs can imitate brain death status, but some aspects of brain stem function, for instance, the pupillary response to light, are preserved. If ingested in large doses, many drugs can cause a partial

Table 4.4 Confirmatory testing for brain death diagnosis

Cerebral angiography (conventional, computerized tomography, magnetic resonance, and radionuclide): absence of intracerebral filling at the level of carotid bifurcation or the circle of Willis
Electroencephalography: absence of electrical activity during at least 30 min of recording (note that the intensive care setting can result in an altered reading due to electronic artifacts)
Transcranial Doppler ultrasonography: small systolic peaks in early systole without diastolic flow showing very high vascular resistance associated with abnormal increased intracranial pressure (~10 % of patients may not have temporal insonation windows because of skull thickness)
Nuclear brain scanning: brain death is confirmed by the absence of isotopic uptake in cerebral parenchyma

loss of brain stem reflexes. A practical approach to drug/toxin exposure can be as follows:

(a) Drug or poison is known, but the substance cannot quantified: patient should be observed for a period at least four times the elimination half-life of the substance.
(b) Drug not known, but there is high suspicion: patient should be observed for 48 h to observe any change in brain stem reflexes; if there is no change, a confirmatory test must be performed [28].

The locked-in syndrome is usually due to the destruction of the base of the pons. The patient cannot move the limbs, grimace, or swallow, but blinking and vertical eye movements are preserved because the upper rostral mesencephalic structures are not involved. Consciousness persists because the tegmentum and the reticular formation are not damaged [26, 29]. This syndrome is often caused by an acute embolism of the basilar artery. Another pathology that mimics brain death is the reversible Guillain–Barré syndrome involving all the peripheral and cranial nerves. The progression can be recorded over a period of days [30].

Confirmatory testing is required by law in several European, Central and South American, and Asian countries; in Sweden, only cerebral angiography is required, and in the United States, the selection of tests is up to the physician [26]. In Italy, brain death is diagnosed according to the following criteria established by Italian law [31]: (a) deep coma; (b) absence of brain stem reflexes; (c) absence of motor responses after painful stimuli in trigeminal areas; (d) apnea ($PaCO_2 > 60$ mmHg); (e) flat electroencephalogram; (f) observation lasting 6 h for adults, 12 h for children younger than 5 years of age, and 24 h for newborns and infants younger than 2 months of age; and (g) cerebral blood flow test to demonstrate the arrest of cerebral circulation when factors affecting clinical evaluation and/or electroencephalography are present (e.g., toxic, metabolic factors, or sedative administration). Table 4.4 shows the main confirmatory testing for brain death diagnosis.

Two models of brain death are widely accepted: whole brain death and the death of the brain stem. For this reason, there are different brain death criteria in different countries: whole brain death is accepted by the United States, Italy, and most European countries, whereas brain stem death has been adopted first by the United Kingdom [31–37]. When whole brain death is considered, only cerebral flow examinations (angiography and SPECT) are suitable and are considered the gold standard [35].

When the clinical criteria of brain death have been diagnosed, the physician should inform the close relatives and discuss organ donation with them. After the first clinical examination of the patient, an observation period, usually 6 h for adults and children >1 year old, is organized to rule out any clinical signs that are incompatible with brain death. A clinical assessment is repeated. In some individuals, cranial or cervical lesions, hemodynamic instability, or other reasons may preclude a definitive clinical assessment. In these cases, a confirmatory test is mandatory to diagnose brain death.

Different legal definitions of death have evolved in different countries over time. In Europe, the United States, and almost worldwide, the following two types of donation after death are commonly employed: (a) donation after brain death (DBD) and (b) donation after circulatory death (DCD).

Although kidney transplantation in the 1950s and 1960s was primarily from live donors, at the dawn of transplantation, all organs were retrieved from patients immediately after cardiorespiratory arrest, i.e., from "non-heart-beating" donors (NHBDs) that are recently better defined DCD. Upon the acceptance of the brain death definition, "heart-beating" donors rapidly became the primary source of organs for transplantation. However, the number of heart-beating donors is now progressively decreasing due to the great improvements in the diagnosis and treatment of severe brain injuries, and fewer young people are dying from severe trauma or catastrophic cerebrovascular events [7, 38, 39]. The number of DCD is slowly increasing worldwide, and in the United Kingdom, a steady increase in DCD activity from 5.6 % (42/745) in 2001/02 to 36.93 % (373/1010) in 2010/11 was reported [39, 40].

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