Brain death criteria

The neurological determination of death

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ABSTRACT

تعني الوفاة الدماغية انعدام في جميع وظائف الدماغ وجذعه. يتم تشخيص الوفاة الدماغية سريرياً، ويحتاج تحديدها إلى وجود خللٍ عصبي حاد لا رجعة منه، ولكي يكون تقييم الوفاة الدماغية دقيقاً، يجب التأكد من عدم وجود تسمم دوائي، خلل كيميائي بالدم، أو انخفاض في درجة حرارة الجسم. يجب تحديد الوفاة الدماغية من قبل أثنين من الأطباء الأستشاريين على الأقل، ومن الأفضل مشاركة عضو مستقل وغير مشارك بالعناية بالمريض أو عملية زرع الأعضاء في هذا التقييم. تهدف هذه المقالة إلى تقديم مراجعة حديثة عن عملية التقييم لتحديد الوفاة الدماغية، علماً أنه يجب التأكد من انعدام جميع وظائف الدماغ وجذعه عن طريق الفحص العصبي، والمتضمن الاستجابة للمحفزات الخارجية وانعكاسات جذع الدماغ، كما يجب التأكد من عدم وجود قدرة على التنفس في جميع الحالات، أما في حالة تعذر ذلك، فيجب القيام بفحوصات أضافية للتأكد من وجود الوفاة الدماغية. من أهم الفحوصات التي يتم إجرائها للتأكد من وفاة المريض دماغياً هي: تخطيط الدماغ والأشعة النووية، علماً أن تخطيط الدماغ مفيد في حالات الأطفال، انخفاض ضغط الدم، أو في حالات ارتفاع ضغط الدماغ، أما الأشعة النووية فهي مفضلة في حالات وجود تسمم دوائي، خلل كيميائي بالدم، أو انخفاض في درجة حرارة الجسم.

Brain death implies the permanent absence of all cerebral and brainstem functions. The diagnosis of brain death is usually made clinically. The criteria require the occurrence of acute and irreversible CNS insult. Drug intoxication, poisoning, metabolic derangements, and hypothermia should be corrected for accurate brain death evaluation. At least 2 expert examiners are required to make the brain death determination. It is advisable to involve an independent examiner not involved in the patient's care or the recovery of donated organs. The objective of this article is to present updated guidelines for the process of brain death determination. All brain and brainstem functions should be absent on neurological examination including cerebral response to external stimuli and brain stem reflexes. An apnea test should be performed in all patients. However, if the clinical criteria cannot be applied, other confirmatory ancillary tests are required, particularly EEG, and radionuclide scan. They are also needed to supplement the clinical assessment in young children. An EEG is more reliable in the setting of hypotension or with disorders that lower intracranial pressure. While tests of brain blood flow are preferred in the setting of hypothermia, metabolic, or drug confounders.

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Death is the irreversible cessation of all critical body functions.[1] The brain is vital for integrating these critical body functions. Therefore, death of the brain is equivalent to whole body death.[2] However, survival of other tissues or organs in isolation may continue beyond brain death. Brain death implies the permanent absence of all cerebral and brainstem functions. The term is specific and should not be used loosely to describe patients with severe brain damage or those in persistent vegetative states. Although specific details of diagnostic criteria vary in different countries, the fundamental definition of brain death has remained almost the same. The diagnosis of brain death is highly related to organ donation. Most countries have specific brain death diagnostic mandates when applied to organ donation; however, general criteria are not always mandated. As well, most clinicians do not constantly adhere to the published guidelines.[3,4] The variation of clinical practice is even greater in the pediatric field.[5] The objectives of this article are to review these guidelines and specific brain death criteria as applied to clinical practice. Clinical, neurophysiological, and neuroimaging guidelines will be reviewed and summarized.

Clinical criteria. The diagnosis of brain death is usually made clinically. The criteria require the presence of acute and irreversible CNS insult with the absence of all brain and brainstem functions on neurological examination (**Table 1**). At least 2 expert examiners are required to make the brain death determination.[3] The mandated number of examiners varies according to the country's law, ranging from 1-4.[6] As well, some countries specifically require one of the physicians to be specialized in neurology. However, all examiners making the diagnosis of brain death should be familiar with the clinical criteria and comfortable in performing all aspects of the examination. It is advisable to involve an independent examiner not involved in the patient's care or the recovery of donated organs.[7] Once the assessment is complete, a follow-up evaluation is mandatory in most, but not all, countries. The duration between the 2 assessments is age dependent (**Table 2**). It should be no less than 48-hours for infants 7 days to 2 months of age, 24 hours for those between 2 months to one year, and 12 hours for those between 1-18 years. An observation period for adults is optional in many countries, however, 6 hours is often recommended, particularly for organ donation. A longer period of observation, up to 24 hours, is advisable in patients with potentially reversible hypoxic ischemic encephalopathy.[3] Generally, it is advisable to think of the process of brain death determination in 4 stages: etiology, clinical setting, examination, and apnea testing (**Table 1**).

1. Etiology. Before starting the assessment, clinical or neuroimaging evidence of an acute and permanent CNS catastrophe that is compatible with the clinical diagnosis of brain death should be established. Trauma and hypoxic ischemic insult are the most common causes.[8,9] However, any condition causing irreversible widespread brain injury can lead to brain death including infections or tumors. Complicating medical conditions that may confound the clinical assessment, such as severe electrolyte or acid-base disturbances, should be corrected for accurate evaluation. As well, potentially treatable or reversible drug intoxication or poisoning should also be excluded.

2. Clinical setting. Normal body temperature and blood pressure are needed for accurate evaluation. Core temperature ≥36.5ºC, systolic blood pressure ≥90 mm Hg, and normovolemic status are prerequisites.[3] Hypothermia and hypotension may confound the diagnostic assessment of brain death, however, there is little evidence for a choice of threshold temperature. Therefore. the 2006 Canadian forum recommendations substituted 34ºC as a standard.[10] The patient should also be off sedation or neuromuscular paralysis.

3. Clinical examination. Adequate skills in performing the neurological examination are mandatory for proper assessment.[11] The examination must demonstrate deep unresponsive coma with absent cerebral and brainstem functions including no motor response to pain stimulus above the neck, no pupillary

Table 1 - Brain death criteria.

Etiology
Established acute and irreversible CNS insult (trauma, hypoxia, ischemia)
Exclude drug intoxication or poisoning that can be treatable or reversible
Exclude other complicating or transient medical conditions that may affect the clinical assessment (severe electrolyte or acid-base disturbances)
Clinical setting
No hypothermia (temperature ≥36.5ºC)
No hypotension (systolic blood pressure ≥90 mm Hg)
No sedation
No neuromuscular paralysis
Clinical examination
Deep unresponsive coma
No motor response, including response to pain stimulus above the neck
No pupillary light reflex (midposition or dilated)
No cough with tracheal suctioning
No corneal or gag reflexes
No oculovestibular reflexes (caloric response)
Apnea testing
No respiratory response ($PaCO_2$ >60 mm Hg or 20 mm Hg more than baseline)

Table 2 - Differences between children and adults in the application of brain death criteria.

Criteria	Children	Adults
Age limit	Older than 7 postnatal days	Any age
Examination maneuvers	In addition to criteria in table 1: Oculocephalic reflex (doll's eye), sucking reflex, rooting reflex	As in table 1
Serial examinations	Mandatory	Optional*
Interval between assessments	48 hours (ages 7 days-2 months) 24 hours (ages 2 months-1 year) 12 hours (ages 1-18 years)	6 hours
Ancillary tests	2 positive (ages 7 days-2 months) 1 positive (ages 2 months-1 year) Optional after age 1 year**	Optional**

*Required if organ donation is considered or in hypoxic ischemic insult,
**Required only for clinical uncertainty or confounding factors

Table 3 - Common spinal cord or peripheral movements in brain dead patients.

Facial twitches
Subtle, semi-rhythmic facial movements arising from the denervated facial nerve
Finger twitching
Finger flexor movements
Arm pronation
Upper limb pronation extension reflex
Tonic neck reflexes "Lazarus sign"
Passive neck displacements, especially flexion, maybe accompanied by complex truncal and extremity movements including adduction at the shoulders, flexion at the elbows, supination or pronation at the wrists, flexion of the trunk ("sitting up" type movements), and neck-abdominal muscle contraction or head turning to one side
Truncal movements
Asymmetrical opisthotonic posturing of the trunk and preservation of superficial and deep abdominal reflexes
Abnormal Babinski
Triple flexion response with flexion at the hip, knee, and ankle with foot stimulation
Undulating toe sign
Alternating flexion-extension of the toes with passive displacement of the foot

light reflex (midposition or dilated), no corneal reflexes, no oculovestibular reflexes (caloric responses), no jaw jerk, no gag reflex, no cough with suctioning, and apnea as demonstrated by apnea test. In addition, oculocephalic (doll's eye maneuver), sucking, and rooting reflexes should be absent in children. The depth of coma must be assessed by documenting absent alerting response and no spontaneously, or stimulus induced cortically originating movements. These include complex and purposeful movements, such as withdrawal or facial grimacing. Decerebrate and decorticate posturing are also originating from the brain and therefore should not be seen in brain death. Spontaneous, simple, non-purposeful movements originating from the spinal cord or peripheral nerve may occur in brain death. They are relatively common and may be triggered by tactile stimuli.[12,13] They result from peripheral denervation or loss of cortical inhibitory input on lower motor neurons. Examples of these non-significant movements are listed in **Table 3**. Finally, note that seizures are cortical in origin and therefore should not occur with brain death.

4. Apnea testing. The apnea test is performed after all other criteria for brain death have been met. A positive apnea test demonstrates absence of respiratory response to a $PaCO_2$ >60 mm Hg or 20 mm Hg greater than baseline values. Simply disconnecting the ventilator is frequently associated with severe hypoxemia, bradycardia, and hypotension. These can be obviated by increasing inspired oxygen before and during the test. Preoxygenation eliminates respiratory nitrogen stores and accelerates oxygen transport.[3] The fraction of inspired oxygen should be 1.0 for 10 minutes, up to a maximum PaO_2 of 200 mm Hg. The patient is then disconnected from the ventilator. Oxygen is provided by a tracheal cannula at 6 L/minute. Visual observation for detecting respiratory movement should be carried out for 10 minutes. The $PaCO_2$ should be remeasured just prior to reconnection to the ventilator to confirm that the target level was achieved. The test may need to be aborted because of hypotension or bradycardia. This may suggest inadequate preoxygenation, inadequate oxygenation during the test, or poor baseline cardiopulmonary status. Further confirmatory ancillary tests are necessary in this situation.

Ancillary tests. An accurate and comprehensive clinical examination is sufficient in determining brain death. Sometimes the clinical assessment cannot be accurate or complete. These situations include: when the cranial nerves cannot be adequately examined, when neuromuscular paralysis or sedation was used and is slow to clear due to multiorgan failure, and when the apnea test cannot be completed. In these situations, ancillary tests are necessary.[14] Confirmatory ancillary testing is also required for infants less than one year. At least 2 positive tests are required routinely for infants less than 2 months of age and one positive test for those between 2 months to one year of age (**Table 2**). Some countries mandate the routine use of a confirmatory test to supplement the clinical examination in older children and adults.[6] Therefore, such ancillary testing should be highly suggestive of total and irreversible brain insult with no "false positives" results. Such a test should also be readily available, safe, and applied in all medical centers. Unfortunately, no currently available test for brain death meets all these criteria. Studies examining their utility are limited with small biased samples limiting the detection of false-positive results. Individual tests have different strengths and weaknesses in different clinical settings, which may guide their selection. Ancillary tests used in confirming brain death are divided in 2 subgroups; neurophysiological and brain blood flow studies.

1. Clinical neurophysiological studies. Electroencephalography (EEG). The EEG is the single most useful electrophysiological test of brain function.[15] Electrocerebral silence (flat EEG) is expected in brain death. Technically, the EEG should contain no electrical cortical rhythms of >2 mV during a 30-minute recording.[16] A specific EEG montage with long interelectrode distance and at least 18-channel recording is recommended. The EEG is the most commonly ordered confirmatory test and is an essential part of the American criteria for the diagnosis of brain death in young children.[17] However, note that the EEG summates

synaptic potentials from the cerebral neocortex and does not reveal potentials from subcortical structures, such as the brain stem or thalamus. Therefore, the EEG may be flat or isoelectric in the presence of viable neurons in the brain stem. The EEG is also vulnerable to confounders, and may be isoelectric in cases of sedation, hypothermia, or metabolic disturbances. In these cases, a flat EEG recording is falsely positive.[18] In addition, electrical artifacts are frequently recorded, especially in the intensive care unit. Artifacts may be mistaken by the less experienced interpreter for residual cortical activity.

Evoked potentials. Somatosensory evoked potentials (SSEPs) and brainstem auditory evoked potentials (BAEPs) are used infrequently as ancillary tests.[19] In SSEPs, the bilateral absence of the parietal sensory cortex responses (N19-P22) in response to median nerve stimulation is supportive of brain death. The absence of brainstem responses to an auditory stimulus (Waves III to V) in the presence of preserved cochlear response (Wave I) is required for a BAEP result to support the diagnosis of brain death. These tests activate discrete and restricted sensory pathways in the brainstem. Therefore, they do not test the functional integrity of other CNS structures. As well, peripheral lesions outside the CNS may affect their results. Falsely positive results, particularly in patients with primary brainstem pathology, have been reported.[20] However, components of SSEPs and BAEPs are minimally affected by sedative drugs and anesthetics.[21]

2. Brain blood flow studies. Tests demonstrating absent blood flow to the brain are generally considered confirmatory of whole brain death.[14] Brain death is usually associated with increased intracranial pressure (ICP) due to tissue edema or mass effects. Lack of cerebral blood flow occurs when the ICP exceeds the systemic arterial pressure flow. Tests of cerebral blood flow include nuclear medicine, cerebral angiography, transcranial Doppler, magnetic resonance angiography (MRA), and computed tomographic angiography (CTA). These tests are not confounded by drugs, metabolic disorders, or hypothermia. However, the systemic blood pressure should be adequate. The presence of some arterial blood flow in the intracranial compartment does not always preclude the diagnosis of brain death. This may occur if the intracranial pressure is lowered, such as in patients with skull fractures, craniotomy, ventricular drain, or in infants with open cranial sutures. Acknowledging the existing limitations of these tests, further research validating current and evolving techniques of brain blood flow imaging are needed.

Nuclear medicine. The 2 main radionuclide techniques used in the evaluation of brain death are radionuclide angiography with nonlipophillic agents and parenchymal imaging using lipophilic agents.[22] The most commonly used radionuclide tracer is 99mTc-labeled hexamethylpropyleneaminoxime (HMPAO). The tracer penetrates into the brain parenchyma in proportion to regional blood flow and shows no significant redistribution for several hours, making it easy to perform and interpret the images. The absence of isotope uptake ("hollow skull phenomenon") indicates no brain perfusion and supports the diagnosis of brain death.[23] The test is useful in pediatric patients with limited false-positive and false-negative results.

Cerebral angiography. Traditional 4-vessel cerebral angiography is the "gold standard" among cerebral blood flow tests for brain death. However, the test is invasive and requires transportation to the radiology department. Cerebral angiography usually demonstrates absent blood flow beyond the carotid bifurcation or Circle of Willis. Contrast stasis or delayed filling in intracranial arteries is an earlier stage proceeding absent filling.[24] A false-negative result showing some normal blood flow in some intracranial vessels may occur rarely with lowered intracranial pressure (craniotomy, VP shunts, or infants with open sutures). Therefore, cerebral angiography is not only invasive, but also risky, and may be inaccurate.

Transcranial Doppler. Transcranial Doppler (TCD) is an innovative, safe, and noninvasive tool for the bedside monitoring of static and dynamic cerebral blood flow.[25,26] Small systolic peaks without diastolic flow or a reverberating flow pattern suggests high vascular resistance and supports the diagnosis of brain death. Temporal bone thickening precludes the evaluation in up to 25% of patients. This and other technical limitations may give false positive results and therefore limit the value of TCD.[27] Despite the currently reported sensitivity of 70% and specificity of 97%, the procedure requires further study, particularly in young children.[28]

Magnetic resonance angiography (MRA). Absence of arterial blood flow on MRA supports the diagnosis of brain death. Small case series suggest that it may be a useful test in brain death.[29,30] The MRA is problematic in unstable patients as the patient is required to lie flat for a long time. There are also practical difficulties in performing close clinical monitoring of these unstable patients. The MRA may prove more useful in the future.

Computed tomographic angiography (CTA). The CTA and CT perfusion are more invasive than MRA requiring contrast injection. Several case reports document findings of absent cerebral circulation perfusion in patients with brain death.[31,32] The test needs further study before further recommendation.

Misdiagnoses. Rarely, brain death can be misdiagnosed if the previously described protocol were not followed, particularly by less experienced physicians. Hypothermia, drug intoxication, and

metabolic encephalopathy can present with severe brain and brainstem dysfunction simulating brain death. Therefore, they should be corrected before such declaration is made. Occasionally, locked-in syndrome and severe Guillain-Barré syndrome may produce a neurological examination consistent with brain death. The locked-in syndrome is a consequence of focal insult to the base of the pons, usually by embolic occlusion of the basilar artery.[33] Consciousness is preserved; however, the patient cannot move the limbs, trunk, or face. Only voluntary blinking and vertical eye movements remain intact. Patients with this syndrome have been mistakenly believed to be unconscious.[34] Patients with primary brainstem pathology who are believed to be brain dead should be carefully examined to ensure that they are not locked-in. Detailed history taking and careful neurological examination will easily exclude Guillain-Barré syndrome. All potential brain death mimics should not be mistaken for brain death if the clinical brain death criteria are applied.

Communicating the news to families. Once the diagnosis of brain death is confirmed, such information should be communicated to the family and relatives. Communicating such news is often both difficult and emotionally unwelcome.[35] Most physicians do not feel comfortable in such difficult situations. At the same time, it is important that the transfer of such information is carried out well as the manner in which bad news is conveyed to relatives can significantly influence their emotions, beliefs, and attitudes towards the medical staff, and the future.[35] Most families find the attitude of the news giver, combined with the clarity of the message and the news giver's knowledge to answer questions as the most important aspects of giving such bad news. Note that the perception that death has occurred differs from one person to another. The diagnosis of brain death is intricately linked to the issue of organ donation and may influence a family member's decision making.[36] Bereaved family members approached to donate the organs of their brain dead relative should have a good understanding of what this diagnosis means. The reliability and differences between cardio-pulmonary versus brain based criteria of death should be explained.[37] In many developed countries, people can decide on whether they will be donors upon getting their driver license. This will ease the pressure on their relatives who may have difficulty accepting the responsibility of making such decision at the time of death. From a parent's perspective, brain death and organ donation are neither morally or medically straightforward concepts.[38] There is clearly a strong need for more research and clinical training in communication issues regarding brain death and end-of-life care with families in critical care situations.[39]

Prognosis. Brain death rarely lasts for more than a few days before it is followed by whole body death. Brain ischemia leads to sympathetic nervous system collapse with vasodilatation and cardiac dysfunction.[40] Pulmonary edema and diabetes insipidus are common early consequences of brain death and may precipitate cardiopulmonary failure.[41] Rare cases of prolonged somatic survival of clinically brain dead adults have been reported.[42] However, the diagnosis of brain death becomes doubtful in the face of prolonged clinical stability, particularly in pediatric patients.[43] Some families have religious beliefs that oppose the equivalence of brain death with death. In Saudi Arabia, a religious law (Islamic Fatwa) allows physicians to discontinue life support over the family's objection in patients with documented brain death. However, decision delay, further education, support, and negotiation are advocated in such situations.[44,45] The potential for organ donation may offer comfort to some bereaved families, however, it should not be the impetus for the diagnosis of brain death.

In conclusion, brain death is the complete and irreversible loss of cerebral and brain stem functions. It is considered to be equivalent to whole body death. The diagnosis of brain death is usually made clinically; however, certain prerequisites are needed. These include an established acute and permanent cause, and exclusion of drug intoxication, poisoning, metabolic derangements, and hypothermia. The neurological examination must demonstrate deep unresponsive coma, no cerebral response to external stimuli, and absent brain stem reflexes. An apnea test should be performed in all patients meeting all other brain death criteria. Confirmatory ancillary tests are required when the clinical criteria cannot be applied and to supplement the clinical assessment in young children. The EEG and radionuclide scan are the 2 most commonly used tests for brain death confirmation. The EEG is more reliable in the setting of hypotension, craniotomies, or other factors that lower intracranial pressure. While tests of brain blood flow are preferred in the setting of hypothermia and metabolic or drug confounders.

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