PRACTICE GUIDELINES

Guidelines for the Diagnosis of Brain Death

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Brain death is defined as the irreversible loss of the capacity for consciousness combined with the irreversible loss of all brainstem functions including the capacity to breathe.[1,2] Brain death is equivalent to death of the individual, even though the heart continues to beat and spinal cord functions may persist.[1-3]

Guidelines for organ transplantation and the removal of organs from brain-dead donors is a separate issue that is not addressed in this document. Such procedures must respect provincial and institutional guidelines. As a general rule, those individuals who assess patients for brain death should not be part of the transplant team.

Brain death must be determined clinically by an experienced physician and in accord with the accepted medical standards.[1] Thus the guidelines described below are recommendations based on current medical information and experience. As knowledge advances, it can be anticipated that further revisions will be necessary. Because of the major consequences of the diagnosis of brain death, consultation with other physicians experienced in the relevant clinical examinations and diagnostic procedures is usually advisable.

Brain death can usually be diagnosed reliably by clinical criteria alone. However, there are special circumstances when these are not suitable and cannot be applied. These are discussed below under "Special Circumstances" and "Laboratory Tests".

Guidelines

1) An etiology has been established that is capable of causing brain death and potentially reversible causes have been excluded (see Comment 2 below.)

2) The patient is in deep coma and shows no response within cranial nerve distribution to stimulation of any part of the body. No movements such as cerebral seizures, dyskinetic movements, decorticate or decerebrate movements arising from the brain should be present (see 1a below.)

3) Brain stem reflexes are absent (see 1b, below.)

4) The patient is apneic when taken off the respirator for an appropriate time (see 1c below.)

5) The conditions listed above persist when the patient is reassessed after a suitable interval (see 2 below.)

6) There should be no confounding factors for the application of clinical criteria (see 1c, 2 and Special Circumstances below.)

Comments

1. Cessation of brain function

The clinical absence of brain function is defined as the profound coma, apnea and the absence of brain stem reflexes.

a) Coma The patient should be observed for spontaneous behaviour and response to noxious stimuli. In particular, there should be no motor response within cranial nerve distribution to stimuli applied to any body regions. There should be no spontaneous or elicited movements (dyskinesias, decorticate or decerebrate posturing or epileptic seizures arising from the brain). However, various spinal reflexes may persist in brain death.

b) Brain-stem reflexes Pupillary light, corneal, vestibulo-ocular and pharyngeal reflexes must be absent. The pupils should be midsize or larger and must be unreactive to light. Care should be taken that atropine or related drugs that could block the pupillary light reflex have not been given to the patient. The vestibulo-ocular reflexes should be tested with caloric stimulation while the head is 30° above the horizontal. In adults a minimum of 50 ml of ice water should be used. A minimum of 5 minutes should be allowed between testing on each side. Grimacing or other motor response to corneal stimulation or pharyngeal or tracheal suctioning is incompatible with brain death.[1,4]

c) Apnea Apnea testing requires the availability of blood gas measurement. It is recommended that a PaCO2 of ≥ 60 mm Hg be achieved to ensure that an adequate stimulus is presented to the respiratory centre.[5] It is also suggested that the arterial or capillary blood should be acidemic (pH < 7.28) by the end of the apnea test. The following prerequisites are recommended: i) core temperature should be at least 32.2°C, preferably > 36.5°C, to allow an adequate rate of rise of PaCO2. (Great caution must be exercised in patients with subnormal body temperatures. Further, in chronic retainers of carbon dioxide, the apnea test may not be valid.); ii) systolic blood pressure should be ≥ 90 mm Hg in adults and within normal limits for age in infants and children; iii) the patient should be euvolemic; iv) an initially normal PaCO2 before apnea testing is begun (40 ± 5 mm Hg); v) preoxygenation with 100 oxygen allowing a PaO2 > 200 mm Hg. In performing the apnea test, it is suggested that 100% oxygen is delivered via a cannula placed in the trachea, or at the level of the carina, while the ventilator is stopped. The arterial PaO2, PaCO2 and pH should be checked at 8-10 minutes. The apnea test is positive if no respirations are observed over the 8-10 minutes of observation, provided that the PaCO2 rises to greater than 60 mm Hg.[1,3,6]

2. Irreversibility

Cessation of brain function is determined to be irreversible when: the proximate cause of the coma is known and is capable of causing neuronal death; the loss of brain stem function is total and constant over time; reversible causes of brain dysfunction have been excluded. Drug intoxication (particularly barbiturates, sedatives and hypnotics), treatable metabolic disorders, hypothermia (temperature less than 32.2°C), shock and peripheral nerve or muscle dysfunction due to disease or neuromuscular blocking agents must be excluded. Neuro-imaging, in

selected cases, may be useful in documenting a structural cause and determining the extent of anatomical damage.

Re-evaluation is essential to ensure that the nonfunctioning state of the brain is persistent and to reduce the possibility of error. Depending on the etiology, the interval between such examinations may be as short as 2 hours or as long as 24 hours; observation for 24 hours is usually recommended to confirm brain death due to anoxic-ischemic insults (e.g., post-cardiac arrest). In situations where brain death is declared for purposes of organ transplantation, local regulations may stipulate specific intervals for reassessment.

Special Circumstances

Neonates and young children In children with a conceptional age of 52 weeks or older (more than 2 months post-term) the adult clinical criteria can be applied. Clinical criteria alone are not sufficient in the determination of brain death in infants under this age.[7-9] The basic tenets accepted in adults that apply to children include: (i) the importance of excluding remediable or reversible conditions, specially toxic and metabolic derangement and the effects of sedative drugs, paralytic agents, hypothermia and hypotension, (ii) physical examination criteria must be satisfied (outlined under "comments" above) and (iii) irreversibility must be ensured by re-evaluation at specified intervals. It is recommended that: (a) for term newborns (greater than 38 weeks gestation) and young infants, aged 7 days to 2 months, that the clinical examination and a radionuclide brain flow study be done, (b) for those 2 months to 1 year, two examinations and EEGs separated by at least 24 hours was suggested; a repeat examination and EEG would not be necessary if a concomitant radionuclide angiographic study failed to visualize cerebral arteries, and (c) in those over 1 year of age, an observation period of at least 12 hours is recommended. However, in those comatose due to hypoxic-ischemic encephalopathy, at least 24 hours of observation is suggested. The validity of the application of clinical criteria to preterm infants is still uncertain. Further guidelines are needed. Clearly additional supportive investigative tests, e.g., those of brain perfusion, are needed to substantiate the diagnosis of brain death in this group.

Inability To Apply The Clinical Criteria Some clinical situations may preclude the valid application of the listed clinical criteria, e.g., trauma to the eyes, middle or inner ear injuries, cranial neuropathies, severe pulmonary disease and some cases of profound metabolic and endocrine disturbances. In these situations, the most reliable means of determining brain death is the demonstration of the absence of brain perfusion. Some conditions may mimic brain death, e.g., hypothermia, drug intoxication, the use of neuromuscular blocking and anticholinergic agents and shock. These should be excluded or reversed before applying the clinical criteria. In some situations, the use of reliable laboratory tests for brain perfusion, providing the blood pressure is normal, are utilized to confirm the diagnosis of brain death.

Laboratory Tests

Although brain death can be established reliably by clinical criteria alone, special tests can be used to support the clinical diagnosis. These are discussed below.

Cerebral angiography A selective 4-vessel angiogram is done with the iodinated contrast medium injected under high pressure in both the anterior and posterior circulations. It should be assured that the mean arterial pressure is at least 80 mm Hg. In brain death no intracranial perfusion other than an occasional filling of the superior sagittal sinus is seen. The lack of intracranial perfusion other than filling of the superior sagittal sinus is strongly confirmatory of brain death.[10,11]

Radionuclide scanning This is being increasingly used as an alternative to cerebral angiography as a test of cerebral perfusion. Two–planar imaging using a radioactively-labeled substance that readily crosses the blood-brain barrier (such as Technetium-99m hexamthylproplyeneamineoxme [^{99m}Tc-HMPAO] is recommended.[12] In brain death no uptake is seen in the brain parenchyma. Alternatively, the rapid bolus injection of serum albumin labeled with technetium 99m is given, followed by imaging with a gamma camera. In brain death there is lack of penetration of ^{99m}Tc-HMPAO into the brain parenchyma or no intracranial perfusion seen in the arterial phase following the bolus injection of radio-labeled albumin. Late filling of the superior sagittal sinus may occur, however.

Transcranial Doppler ultrasonography Using a 2 MHz pulsed Doppler instrument, the intracranial arteries are insonated bilaterally, including the middle and/or anterior cerebral arteries and the vertebral or basilar artery.[13] The finding of absent diastolic or reverberating flow or small systolic peaks have been reported in brain death. The absence of transcranial Doppler signals cannot be taken as evidence of brain death, as 10% of people do not have temporal insonation windows.[5] The test should be performed and interpreted by qualified individuals with considerable experience.

Other imaging tests Although magnetic resonance imaging (MRI) techniques hold promise, they have not been sufficiently studied or validated to be used as the sole confirmatory test at this time. Neuro-imaging, e.g., with MRI or computed axial tomography, may help to confirm the structural nature and extent of damage in selected cases.

Electroneurophysiological tests The electroencephalogram (EEG) is of some confirmatory value and may have a place in selecting certain individuals, e.g., very young children, for apnea testing. The EEG does not, however, adequately assess brainstem function and should not be used as the sole confirmatory test for brain death. The use of evoked potentials, including brainstem auditory and somatosensory evoked potential testing, has promise, but these have not been sufficiently validated. Furthermore, they are highly dependent on technical quality and require considerable expertise and experience for reliable performance and interpretation.

Atropine test The absence of an increase in heart rate after the intravenous injection of 2 mg of atropine, is confirmatory of the absence of vagal tone and is helpful in confirming dysfunction of the caudal brainstem.[14,15] Although helpful, the atropine test is not sufficient as the sole confirmatory test of brain death. Because of the anticholinergic effects on pupillary reactivity and EEG, the test should be performed after completion of clinical and electroencephalographic testing. Further, the test is not valid in cases of autonomic neuropathy or following cardiac transplantation with denervation of the autonomic fibres to the heart.

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