

BRAIN DEATH DIAGNOSIS

Calixto Machado

Brain death (BD) diagnosis should be established based on the following set of principles, i.e. excluding major confusing factors, identifying the cause of coma, determining irreversibility, and precisely testing brainstem reflexes at all levels of the brainstem. Nonetheless, most criteria for BD diagnosis do not mention that this is not the only way of diagnosing death. The Cuban Commission for the Determination of Death has emphasized the aforesaid three possible situations for diagnosing death: a) outside intensive care environment (without life support) physicians apply the cardio-circulatory and respiratory criteria; b) in forensic medicine circumstances, physicians utilize cadaveric signs (they do not even need a stethoscope); c) in the intensive care environment (with life support) when cardiorespiratory arrest occurs physicians utilize the cardio-circulatory and respiratory criteria. This methodology of diagnosing death, based on finding any of the death signs, is not related to the concept that there are different types of death. The irreversible loss of cardio-circulatory and respiratory functions can only cause death when ischemia and anoxia are prolonged enough to produce an irreversible destruction of the brain. The sign of irreversible loss of brain functions, that is to say BD diagnosis, is fully reviewed. *Acta Medica Medianae 2009; 48(3):25-30.*

Key words: *brain death, signs of death, brain death criteria, transcranial Doppler, multimodality- evoked potentials*

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Introduction

Most authors affirm that the diagnosis of BD is just a clinical assessment, and after the Harvard Committee Report (1,2) most countries and states designed their BD diagnostic criteria (3,9). BD diagnosis should be established based on the following set of principles, i.e. excluding major confusing factors, identifying the cause of coma, determining irreversibility, and precisely testing brainstem reflexes at all levels of the brainstem (9).

Nonetheless, most criteria for BD diagnosis do not mention that this is not the only way of diagnosing death. If a concept of death on neurological grounds is accepted, then BD diagnostic criteria can be only applied in patients under life support assistance in ICUs. Does it mean that when a physician diagnose death in a regular ward (patient is not under life support) applying cardiocirculatory and respiratory diagnostic criteria, or when a forensic specialist diagnose death in a body under criminal circumstances, are we denying a brain-oriented concept of death? (11,12).

Cuba has recently passed a law for the determination and certification of death. The National Commission for the Determination and Certification of Death has accepted a neurological view of death and emphasized that any legislation of death should be completely separated from any norm governing organ transplants (13,14). Hence, the Commission enumerated three possible situations for diagnosing death:

1. Outside the intensive care environment (without life support) physicians apply the cardiocirculatory and respiratory criteria.
2. In forensic medicine circumstances physicians utilize cadaveric signs (they do not even need a stethoscope).
3. In the intensive care environment (with life support) when cardiocirculatory and/or respiratory arrest occurs, physicians utilize the cardiocirculatory and respiratory criteria. When physicians suspect of irreversible loss of brain functions in a heart-beating and ventilatory supported case, BD diagnostic criteria are applied.

This methodology of diagnosing death, based on finding any of death signs, is not related to the concept that there are different types of death. The irreversible loss of cardiocirculatory and respiratory functions can only cause death when ischemia and anoxia are prolonged enough to produce an irreversible destruction of the brain. According to the Commission, there is only one kind of death, based on the irreversible loss of brain functions (11-16).

Signs of death

The diagnosis of death was based on the finding of any of death signs:

- I. Irreversible loss of respiratory function
- II. Irreversible loss of cardiocirculatory functions
- III. Algor mortis (postmortem coldness)
- IV. Livor mortis (postmortem lividity)
- V. Rigor mortis (postmortem rigidity)
- VI. Cadaveric spasm
- VII. Loss of muscle contractions
- VIII. Putrefaction
- IX. Irreversible loss of brain functions

Signs I and II correspond to the classical respiratory and cardiocirculatory functions. Signs III to VIII are related to forensic circumstances, and out of the scope of this review.

Irreversible loss of brain functions (Diagnosis of BD)

As already emphasized, when physicians suspect of irreversible loss of brain functions in a heart-beating and ventilatory supported case, BD diagnostic criteria are applied.

To assess brain functions during BD diagnosis, the clinical neurologic examination is the accepted standard (10,11,16-21).

Preconditions or prerequisites:

1. Coma due to an irreversible acute brain damage of known etiology, affecting both hemispheres and brainstem.
2. At the beginning of neurological examination, the following confounding factors should be excluded:
 - a) unresuscitated shock. Systolic arterial pressure should be over 90 mm Hg;
 - b) hypothermia (core temperature <34 degrees Celsius);
 - c) severe metabolic disorders capable of causing a potentially reversible coma;
 - d) peripheral nerve or muscle dysfunction, and neuromuscular blockade;
 - e) evidence of drug intoxication or poisoning.

Diagnostic Criteria

1. Deep unresponsive coma
2. Absent brainstem reflexes
 - Corneal responses
 - Pupillary responses to light with pupils at mid-size or greater
 - Oculocephalic and oculo-vestibular responses
 - Gag and cough responses
3. Negative Atropine Test
4. Absent respiratory effort confirmed by the apnea test
5. Periods of observation: 6 hours. In cases of acute hypoxic-ischemic brain injury, clinical evaluation should be delayed for 24 hours subsequent to the cardiorespiratory arrest, or ancillary test could be performed.
6. Confirmatory tests
 - tests to demonstrate a complete cessation of brain circulation: TCD

- confirmatory tests to demonstrate loss of bioelectrical activity: EEG, EP and ERG.

Preconditions or prerequisites:

1. Coma due to an irreversible acute brain damage of known etiology, affecting both hemispheres and brainstem.

It is demanded to have a clear and definite clinical and/or neuroimaging evidence of an acute central nervous system (CNS) insult which is consistent with the irreversible loss of neurological function (8,10,12,22,23).

The loss of function of the brainstem is in a large majority of cases the infratentorial consequence of extremely severe supratentorial damage, resulting in untreatable intracranial pressure. Nevertheless, in some cases, primary brainstem lesions may entirely damage this structure while functioning of the cerebral hemispheres is relatively spared. That can be shown in a number of cases by the presence of a "quasi-normal" activity of the EEG and the visual evoked potentials (24-28). Hence, in primary brainstem lesions we have proposed the use of confirmatory ancillary tests (12).

2. Confounding factors should be excluded:

It is essential to exclude the confounding factors that mimic BD (10,12,29,30).

- a Unresuscitated shock

It is indispensable to apply BD criteria only when blood pressure is with a minimum value of 90 mm Hg. The use of hydration fluids and / or vasopressor drugs might re-establish adequate blood pressure values (10,31,35).

- b Hypothermia (core temperature <34 degrees Celsius).

An inability to regulate temperature, or poikilothermia, is often present in BD. Core temperature results should be obtained through central blood, rectal or esophageal gastric measurement. Most sets of criteria for BD diagnosis demand a body temperature of at least 32.2°C (3,10,12,23,34-38).

The correction of hypothermia before applying criteria of BD is just appropriate, especially in children and alcoholic patients who become hypothermic after mild brain injuries (39). Moreover, it is important for physicians to be aware that subjects are undergoing accidental hypothermia (40).

- c Severe metabolic disorders capable of causing a potentially reversible coma.

Severe metabolic or endocrine abnormalities make BD unreliable (10,23,29,30,41). Metabolic or endocrine derangement including glucose, electrolytes (including phosphate, calcium and magnesium), inborn errors of metabolism, liver or renal dysfunction, etc., may cause a potentially reversible coma. If in the physician's judgment the metabolic abnormality matters, it should be corrected (10,12).

- d Peripheral nerve or muscle dysfunction, and neuromuscular blockade potentially play a role for inducing unresponsiveness in patients,

and it could be a confounding factor in BD diagnosis (42).

- e Clinically significant drug intoxications (e.g., alcohol, barbiturates, sedatives, hypnotics)

CNS-depressant drugs should be ruled out if the clinical history is indicative. It is therefore mandatory that the drug history should be carefully reviewed and any possibility of intoxication being the cause of, or contributing to, the patient's comatose state should preclude a diagnosis of BD (23,48-52).

Criteria

1. Deep unresponsive coma

The diagnosis of deep unresponsive coma demands to find a comatose patient showing a lack of spontaneous movements in addition to an absence of motor responses mediated by stimuli applied within the cranial nerve distribution (3,10,13,17,22,41).

CNS-mediated motor response to pain in any other distribution, seizures, decorticate and decerebrate responses impede BD diagnosis. Some BD individuals may present spinal reflexes or motor responses, confined to spinal distribution, which do not preclude the BD diagnosis (10,23,34,35,39,53).

2. Absent brainstem reflexes

The reflexes mediated by the cranial nerves are main indicators of the brainstem function. Hence, to prove their absence is an indispensable element of BD. The individual significance of each individual brainstem reflex varies in BD diagnosis according to an intrinsic sensitivity of the cranial nerve networks and to the effect of some accompanying factors in brain-dead patients, such as trauma, local edema, dried tissues, intracranial tubes affecting the exploration of reflexes (3,39).

- Pupillary Reflex. This reflex is considered one of the most discriminant reflexes in BD diagnosis (3,10,23,30,34,35,39,54). The Harvard Criteria demanded that pupil be fixed and dilated (2). Mydriatic pupils can be found in BD. The sympathetic cervical spine pathways connected to the pupillodilator muscle remain intact. Nonetheless, afterwards, several authors reported that mydriasis is not essential and that often small or medium-sized pupils are found in brain-dead cases (3,36-38).
- Corneal reflex. This is also one of the most discriminant reflexes in BD diagnosis. A bilateral or unilateral response of eyelid closure and upward deviation of the eye (Bell's phenomenon) indicates preserved brainstem functioning. However, edema or drying of the cornea, severe facial and ocular trauma may avoid a satisfactory stimulus for this reflex (3,10,12,22,39,55-57).
- Oculocephalic and oculo-vestibular responses. The oculocephalic reflex, also known as Doll's eyes response is elicited upon brisk turning of the head from middle position to 90 degrees on both sides. In comatose patients without lesions of the brainstem the eyes normally conjugately deviate to

the other side. In BD, no eye movements are observed (7,11,35).

- Gag and cough response
Pharyngeal (gag), cough, and swallowing reflexes are often difficult to explore because of the presence of tubes in the throat and dryness of the mucosa. Hence, in suspected brain-dead cases cough response is usually explored by passing a catheter through the endotracheal tube and suctioning with negative pressure for several seconds. As these reflexes have their arcs through the medulla oblongata, it is desirable to explore them (3,10,38,58,7,11,35).

3. Atropine Test

The atropine test (AtT) assesses bulbar parasympathetic activity on heart activity in brain-dead patients (59). Ouaknine first proposed to include this as a criterion for the so-called brain-stem death (59-63) The method for this test consists in injecting 2 mg of atropine under continuous monitoring the ECG during 10 minutes. The AtT is considered negative if heart rate does not augment by more than 3% compared with basal ECG records (12,31,60,64-69).

4. Apnea Test

The apnea test (AT) has been considered by some authors as the "*condition sine qua non*" for determining BD, because it provides an essential sign of a definitive loss of brainstem functions. Nonetheless, several authors have expressed their concern about the safety of this procedure, due to potential complications, such as severe hypotension, pneumothorax, excessive hypercarbia, hypoxia, acidosis, cardiac arrhythmia or asystole, which may constrain the examiner to abort the test, thereby compromising BD diagnosis. Nevertheless, when an appropriate oxygen-diffusion procedure is used this technique is safe (12,70,70-79).

Periods of observation:

If BD determination is only based in clinical evaluation, the following periods of observation were proposed by the Cuban Commission (12-16).

- 6 hours if a structural and irreversible CNS insult can be demonstrated by clinical and neuroimaging evidences.
- 24 hours in cases of acute hypoxic-ischemic brain injury.

Periods of observation can be shortened according to medical criteria by the application of confirmatory tests (see chapter of confirmatory tests).

5. Confirmatory tests

Confirmatory tests in BD can be divided in those proving absent cerebral blood flow (CBF) and those that demonstrate loss of bioelectrical activity. We recommend assessing circulatory arrest by transcranial Doppler (TCD), and neuronal function by a neurophysiologic test battery, composed by EEG, multimodality evoked potentials (MEP) and electroretinography (ERG). If TCD fails to validate the absence of CBF, computer tomography angiography can be used to confirm BD diagnosis (13-15,80-84).

Confirmatory tests are recommended to shorten periods of observation according to physicians' criteria and in those conditions interfering with the clinical BD diagnosis. The Cuban Commission proposed that confirmatory tests should be mandatory in cases of patients with primary brainstem lesions undergoing BD diagnosis (12-15).

Brain death and organ transplants

It is commonly believed that the concept of BD evolved to benefit organ transplantation. A historical approach demonstrates that both brain death and transplantation had fully separate origins. Organ transplantation became possible with technical advances in surgery and immunosuppressive treatment (20,85-87). Of course, organ procurement programs have induced a close relationship between organ transplants and BD diagnosis in most countries, and hence, it is extremely important to educate the public to understand

that BD means death of the individual, and the importance of organ donation for transplants. Nonetheless, we have emphasized that a concept of BD should not only be related to organ donation, because a patient dies, whether his/her organs are useful or not for transplants.

Conclusions

It is widely accepted that BD is a clinical diagnosis, and it is currently defined as a complete and irreversible loss of brain function. We have enumerated three possible situations for diagnosing death based on the "signs of death". This methodology of diagnosing death does not mean that there are different types of death. The irreversible loss of cardiocirculatory and respiratory functions can only cause death when ischemia and anoxia are prolonged enough to produce an irreversible destruction of the brain. We fully reviewed the diagnosis of BD as death of the individual.

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DIJAGNOZA MOŽDANE SMRTI

Calixto Machado

Dijagnoza moždane smrti (BD) može se postaviti na osnovu sledećih principa, kao što su: isključivanje glavnih konfuzionih faktora, utvrđivanja uzroka kome, utvrđivanje reverzibilnosti kome i preciznog testiranja refleksa moždanog stabla. Međutim, većina kriterijuma za dijagnozu BD ne uzima u obzir činjenicu da postoje i drugi načini za dijagnozu moždane smrti. Kubanska komisija za determinaciju pokazatelja BD (The Cuban Commission for the Determination of Death) je generalno sagledavala dijagnostiku BD u tri moguće situacije: a) dijagnostika izvan jedinica intenzivne nege (bez sredstava za održavanje života), u kojima lekar primenjuje kardio cirkulatorne i respiratorne kriterijume; b) u situacijama sudsko medicinskog veštačenja, kada se koriste kadaverični znaci (u ovom slučaju nije neophodna čak ni upotreba stetoscopa); c) u jedinicama intenzivne nege (sa opremom za „life support“), kada se nakon kardio-respiratornog aresta koriste kardio-cirkulatorni i respiratorni kriterijumi. Ova metodologija dijagnostikovanja smrti zasniva se na dijagnostikovanju bilo kog znaka smrti i nije vezana za činenicu da postoji više tipova smrtnog ishoda. Ireverzibilni gubitak kardio-cirkulatorne i respiratorne funkcije može usloviti smrtni ishod samo kada su ishemija i anoksija prolongirani dovoljno dugo da izazovu ireverzibilno oštećenje moždanih struktura. Znaci ireverzibilnog gubitka moždanih funkcija, tj. dijagnostika BD, prikazana je u svetlu najnovijih literaturnih podataka u ovom radu. *Acta Medica Medianae 2009; 48(3): 25-30.*

Ključne reči: moždana smrt, znaci smrti, kriterijumi, transkranijalni Doppler, multimodalni-evocirani potencijali