Criteria and practical guidance for determination of brain death in adults (2nd edition)

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Statement: In 2013, we published “Criteria and practical guidance for determination of brain death in adults (BQCC version)” in Chinese Medical Journal (Chin Med J 2013, 126:4786–4790). Since then, China has the standard for the determination of brain death. In order to further promote the brain death related work, Brain Injury Evaluation Quality Control Center of National Health Commission (BQCC) aimed to revise and update “Criteria and practical guidance for determination of brain death in adults”. This 2018 new edition was based on the 5-year clinical practice of brain death determination, BQCC quality control analysis of brain death cases, and the opinions and suggestions of BQCC expert committees, technical committees and advisory committees. We hope that the development of brain death determination will be more standardized and orderly in China.

Part I. Criteria for Determination of Brain Death

I. Prerequisites for determination

A. The cause of coma is known.
B. Exclusion of reversible coma.

II. Clinical diagnosis

The clinical diagnosis of brain death should fulfill all the 3 conditions listed as follows:
A. Deep coma.
B. Absence of brain stem reflexes.
C. No spontaneous respiration (depending on mechanical ventilation to maintain breath completely and apnea test to confirm no spontaneous respiration).

III. Ancillary tests

The diagnosis of brain death should fulfill at least 2 of the 3 confirmatory tests listed as follows:
A. Electroencephalogram (EEG) shows electrical silence.
B. Short-latency somatosensory evoked potential (SLSEP) of the median nerve shows that bilateral N9 and (or) N13 exist, while P14, N18, and N20 are absent.
C. Transcranial Doppler (TCD) sonography shows that the blood flows of the intracranial anterior and posterior circulation demonstrate reverberating flow, small systolic spikes, or the absence of blood flow signals.

IV. Time of determination

If the clinical diagnosis (3 conditions) and confirmatory tests (2 items) all fulfill the criteria for brain death, brain death can be declared. If the clinical diagnosis is not complete, the number of ancillary tests should be increased, and a repeat determination should be performed 6h after the first exam. There should be at least 1 apnea test to confirm a lack of spontaneous respiration. If all tests fulfill the determinative criteria, brain death will ultimately be confirmed.

Part II. Practical Guidance for Determination of Brain Death

Brain death is an irreversible loss of the whole brain function (including the brainstem).
I. Prerequisites

A. The cause of coma is known

Primary brain injuries that can induce coma include brain trauma, cerebral vascular disease, and etc. Secondary brain injuries that can induce coma mainly include anoxic encephalopathy resulting from cardiac arrest, anesthetic accidents, drowning, asphyxia, etc. In comatose patients, a brain death of unknown cause cannot be declared.

B. Exclusion of reversible coma

The cause of reversible coma include acute intoxication, such as carbon monoxide poisoning, alcoholic poisoning, sedative hypnotic poisoning, narcotic poisoning, antipsychotic drug poisoning, and muscle relaxant poisoning; shock; hypothermia (bladder, rectal or pulmonary artery temperature <32°C); severe electrolyte and acid-base disturbance; and severe metabolism and endocrine disturbance, such as hepatic encephalopathy, uremic encephalopathy, hypoglycemic encephalopathy, or hyperglycemic encephalopathy.

II. Clinical evaluation

First, the effects of sedation, analgesia, anesthesia and muscle relaxation drugs should be excluded.

A. Deep coma

1. Examination and determination of the results: On pressing the bilateral supraorbital incisure tightly with the thumb or needling the face, there should be no motor responses on the face. The Glasgow Coma Scale is 3.

2. Pitfalls:

2.1. Any noxious stimulus should be limited in the region of the head and face.

2.2. Deep coma should not be judged carefully if trigeminal nerve or facial nerve damage exists.

2.3. Stimulation below the neck may induce spinal reflexes. The spinal cord below the foramen magnum may survive brain death, so the spinal reflexes or and spinal automatic reflexes might still exist. The spinal reflexes include some physiological reflexes and pathological reflexes. The spinal automatic reflexes mostly related to the stimulating position, such as stimulating the neck, may trigger the rotation of the head; stimulating the upper limb may trigger flexion, extension, lift, pronation, and supination of the upper limb; stimulating the abdomen may trigger contractions of the abdominal wall muscle; and stimulating the lower limb may trigger flexion and extension. Spinal automatic reflexes should be differentiated from the spontaneous movements of limbs. Spinal automatic reflexes are strictly related to the specific stimulating position, while spontaneous movements always occur unilaterally without any stimulation. There should be no spontaneous movements of the limbs in brain death.

2.4. There should be no decerebrate rigidity, decorticate rigidity, and spasm in brain death.

B. Absence of brainstem reflexes

1. Pupillary light reflex

1.1. Examination: Observe a pupillary contraction to a bright light in both eyes. First, illuminate one pupil with lateral light, observe the response of the ipsilateral pupil (direct pupillary light reflex), and then examine the other. Illuminate one pupil, observe the response of the contralateral pupil (indirect pupillary light reflex), and then examine the other. These examinations should be performed repeatedly.

1.2. Determination of the results: No bilateral direct and indirect light reflexes are determined in the absence of a pupillary light reflex.

1.3. Pitfalls: Brain dead patients mostly present bilateral mydriasis (>5mm). However, small-sized or medium-sized pupils can be found in brain death. Therefore, the size of the pupil cannot be the essential condition in brain death. Some factors, such as ocular disease or compound injury of head and face, may influence the determination of pupillary light reflexes, so the results should be analyzed carefully.

2. Corneal reflex

2.1. Examination: Lift one upper eyelid, expose the cornea, touch the edge of the cornea lightly with a cotton swab, rapidly turn the head from one side to the opposite side and observe the movements of the eye. Then, examine the other side.

2.2. Determination of the results: No bilateral blink after the 2-side stimulation of the cornea is determined in the absence of corneal reflex.

2.3. Pitfalls: The absence of a corneal reflex should not be judged when there are weak retractions of the upper and lower eyelids and periocular muscles, even without obvious blinks of the eyes. Especially in conditions of ocular diseases or compound injury of head and face and trigeminal nerve or facial nerve diseases, which may influence the determination of corneal reflex, the results should be analyzed carefully.

3. Oculocephalogryic reflex

3.1. Examination: Hold the head in both hands with the thumbs keeping the eyes open and the patient in a supine position. Rapidly turn the head from one side to the opposite side and observe the movements of the eye. Then, examine the other side.

3.2. Determination of the results: No eyeball movement to the opposite side when the head turns left or right is determined in the absence of an oculocephalogryic reflex.

3.3. Pitfalls: In extraocular muscle palsy or compound injury of head and face, which may influence the
4. Oculovestibular reflex

4.1. Examination: Place a kidney-shaped disk near the external auditory canal to avoid water flowing out. Then, aspirate 20 ml normal saline (0–4°C) into a syringe, slowly irrigate this saline into 1 external auditory canal over 20–30s, and maintain the eyelids separation at the same time. Observe whether there is nystagmus. Then, examine the other side.

4.2. Determination of the results: Observe for 1–3 min after irrigation. No nystagmus is determined in the absence of an oculovestibular reflex.

4.3. Pitfalls: Any damage should be excluded from otoscopy before examination. If there is any damage in otoscopy, the examination should not be performed. Remove blood clots or other obstructions in the ear canals before examination. When there are weak movements of the eyeballs, the absence of an oculovestibular reflex should not be declared. In condition of compound injury of the head and face, the hemorrhage or edema in the eyes may influence the determination of the oculovestibular reflex; the results should be analyzed carefully. This examination is different from the caloric tests used in otorhinolaryngology, which use cold water (20°C) or water at 7°C above and below body temperature for alternative stimulation. The caloric tests used in otorhinolaryngology cannot be used to determine brain death.

5. Cough reflex

5.1. Examination: Stimulate the tracheal mucosa with an aspiration tube longer than the artificial airway to elicit a cough reflex.

5.2. Determination of the results: No cough is determined in the absence of a cough reflex.

5.3. Pitfalls: If there are movements of the chest or abdomen when stimulating, the cough reflex should not be determined.

The determination of brain death should fulfill the absence of all the above 5 brainstem reflexes. If some of the 5 brainstem reflexes cannot be fully performed, the redeterminable items should be repeated at least once (with an interval of 5 min) and ancillary tests should be added.

C. Apnea

Apnea and complete dependence on a mechanical ventilator to maintain ventilation are necessary for brain death determination. Apart from a lack of independent triggering on mechanical ventilation, apnea should be confirmed by the apnea test according to the strict procedures and methods as follows.

1. Prerequisites

1.1. Increase core body temperature to ≥36.5°C.

1.2. Adjust vasopressors to a systolic blood pressure ≥90 mmHg (1 mmHg=0.133 kPa) or the mean arterial pressure ≥60 mmHg.

1.3. Preoxygenate for 10–15 min with 100% oxygen to an arterial partial pressure of oxygen (PaO₂) ≥200 mmHg.

1.4. Adjust the minute volume to an arterial partial pressure of carbon dioxide (PaCO₂) of 35–45 mmHg. If there is chronic hypercapnia, PaCO₂ might be above 45 mmHg. It is emphasized that life support and organ function support should be strengthened before the implementation of the apnea test.

2. Procedure

2.1. Arterial blood gas should be drawn to measure PaCO₂.

2.2. Disconnect the patient from ventilator.

2.3. Place the oxygen tube to the level of the carina through an artificial airway and deliver 100% O₂ at 6 L/min.

2.4. Observe the respiratory movements of the chest or abdomen closely.

2.5. Arterial blood gas should be drawn to measure PaCO₂ for 8–10 min.

2.6. The patient should be reconnected to the ventilator.

3. Determination of the results: If the baseline PaCO₂ is 35–45 mmHg and the test result of PaCO₂ is ≥60 mmHg or 20 mmHg over the baseline without respiratory movements, apnea can be confirmed. If the baseline PaCO₂ is above 40 mmHg and the test result of PaCO₂ is 20 mmHg over the baseline without respiratory movements, apnea can be confirmed.

4. Pitfalls:

4.1. It is necessary to confirm whether there is false mechanical ventilation triggering.

4.2. Abort if there is an obvious decrease in blood oxygen saturation, blood pressure, heart rate, or heart arrhythmia. To avoid the influence of the apnea test on confirmatory tests, this examination should be the last step in determining brain death.

4.3. This test requires at least 2 doctors (1 monitors the breath, heart rate, cardiac rhythm, blood pressure and blood oxygen saturation; the other observes the respiratory movements of the chest or abdomen) and 1 doctor or nurse (manages the ventilator and the oxygen tube and draws arterial blood).

4.4. If the apnea test is not complete, the number of ancillary tests should be increased.
Ill. Ancillary tests

A. Electroencephalogram (EEG)

1. Environmental conditions

1.1. Use a separate power supply. A manostat can be used, if necessary.

1.2. Suspend the use of other medical machines that may interfere with EEG, if necessary.

2. Parameter setting

2.1. Place a minimum of 8 scalp electrodes according to the international 10-20 system: frontal pole Fp1, Fp2; central C3, C4; occipital O1, O2; temporal T3, T4, and reference electrodes at bilateral earlobes or mastoids. Place the grounding electrode at the midpoint of the frontal pole (FPz) and the common reference electrode at the median central point (Cz).

2.2. Interelectrode impedances should be under 10,000 V but over 50 V, and electrode impedances should be matched overall.

2.3. Set the high-frequency filter between 30Hz and 75Hz, the low-frequency filter at 0.5Hz, and the time constant at 0.3s.

2.4. Sensitivity: 2 mV/mm.

2.5. Notch filter: 50Hz.

3. Procedure

3.1. Prepare related items for the EEG test.

3.2. Start the machine and input the patient’s general information. Check the parameter setting. A calibration run should be performed for 10s. Input a 10 mV square wave into the amplifier. The sensitivity should be the same.

3.3. Place the recording electrodes.

3.4. A single recording should be at least 30min.

3.5. Give somatosensory and auditory stimuli during tracing and observe the stimulus-related EEG reactivity.

3.6. Any interferences from the outside, machines, or the patient during tracing should be documented on the record in real time. Both monopole and bipolar information should be recorded.

3.7. Electrocardiography tracing at the same time is essential.

4. Determination of the results: The diagnosis of brain death is supported when the EEG shows electrical silence, that is, no EEG activity over 2 μV.

5. Pitfalls:

5.1. The EEG machine used in the determination of brain death must match the requisite parameters.

5.2. Sedatives and anesthesia usage may influence the analysis of EEG; the result is for information only, and the determination of brain death should be based on other ancillary tests.

5.3. Trauma or edema at the location of placing electrodes may influence the analysis of EEG; the result is for information only, and the determination of brain death should be based on other confirmatory tests.

B. Short-latency somatosensory evoked potential (SLSEP)

1. Environmental requirements:

1.1. The environmental temperature should be controlled between 20°C and 25°C.

1.2. Use a separate power supply. A manostat can be used, if necessary.

1.3. Suspend the use of other medical machines that may interfere with evoked potential, if necessary.

2. Recording techniques:

2.1. Designation of electrode locations: According to the international 10-20 system, use disc electrodes or disposable needle electrodes. C’3 and C’4: 2cm behind the positions of C3 and C4 in the international 10-20 system. C’3 or C’4 is called C’c when stimulating the contralateral side. Fz and FPz: Fz is located at the center of the forehead and FPz is located at the midpoint of the frontal pole. Cv6 is located at the spinous process of the 6th cervical vertebra. CLi and CLc: 1cm above ipsilateral and contralateral side clavicles, respectively.

2.2. The montage listed below requires at least 4 channels (recording electrode-reference electrode). Channel 1: CLi-CLc (N9); Channel 2: Cv6-Fz, Cv6-FPz, or Cv6-CLc (N13); Channel 3: C’c-CLc (P14, N18); and Channel 4: C’c-Fz or C’c-FPz (N20).

2.3. Electrode impedance: ≤5 kΩ (recording electrodes and reference electrodes).

2.4. Placement of the groundwire and impedance: 5cm above the stimulating point.

2.5. Analysis time: 50 ms and 100 ms, if necessary.

2.6. Bandpass: 10-2000Hz.

3. Procedure

3.1. Prepare the related items for the SLSEP test.

3.2. Start the machine, input the patient’s general information, and enter the recording state.

3.3. Place the recording electrodes and reference electrodes.

3.4. Place the stimulating electrodes. Position of stimulating electrodes: 2cm above the midpoint of the wrist...
transverse striation, where the median nerve lies below. Generally, the stimulating current is between 5 mA and 25 mA. If the patient has skin edema at the electrode location or peripheral nerve diseases, the current might increase properly. The stimulus intensity is appropriate to induce the muscles innervated by the retraction of median nerve slightly, that is, the thumb flexes approximately 1 cm. It should be kept unchanged during the examination. Stimulating parameters: The duration of the stimulating square wave is 0.1–0.2 ms, up to 0.5 ms, if necessary. The frequency of stimulation is 1–5 Hz. Stimulate bilateral sides.

3.5. At least 500–1000 averages for each time point make the waveform stable and smooth. Record SLSEP at least twice on each side. This should be performed on one side and then the other side, and the 2 test curves of each side should be saved.

4. Determination of the results: The determination of brain death is supported when the SLSEP shows that bilateral N9 and (or) N13 exist, while bilateral P14, N18, and N20 are absent.

5. Pitfalls:

5.1. Keep the patient’s skin temperature normal (hypothermia may induce prolongation of the latencies).

5.2. Some factors, such as trauma or skin edema at the electrode locations, median nerve diseases, cervical cord lesions, or electromagnetic fields interfere with the environment and may influence the analysis of evoked potentials. The waveforms of SLSEP are for information only in the above conditions, and brain death should be determined according to other confirmatory tests.

C. Transcranial Doppler (TCD)

1. Environmental conditions: No special conditions.

2. Equipment: Transcranial Doppler machine, with a 1.6 or 2 MHz pulse-wave Doppler probe.

3. Parameter settings:

3.1. Establish appropriate output power.

3.2. Set the sampling volume: 10–15 mm.

3.3. Adjust the gaining intensity: Adjust the gaining intensity according to the legibility presented by the frequency spectrum.

3.4. Adjust the speed scale plate: Display the frequency spectrum completely on the screen with an appropriate size. Adjust the baseline: Make both upper and lower frequency spectrums completely visible on the screen.

3.5. Adjust the signal-noise ratio: Make the frequency spectrum clearly visible and decrease the noise as low as possible.

3.6. Scanner speed of screen: 6–8 s.

3.7. Set the Doppler frequency filtering wave to a state of low filtering frequency (≤50 Hz).

4. Checking positions:

4.1. Temporal window: To detect the middle cerebral artery (MCA), place the probe at the area between the superciliary arch and the upper ear edges with a supine body position.

4.2. Occipital window or perioccipital window: To detect the vertebral artery (VA) and basilar artery (BA), place the probe at the foramen magnum just below the occipital tuberosity or near the foramen magnum with a supine body position (head has been raised to position the neck out of the air) or lateral decubitus.

4.3. Ocular window: To detect the contralateral MCA and ipsilateral internal carotid artery (ICA) siphon, place the probe near the closed upper eyelid with a supine body position.

5. Recognition of the arteries:

5.1. MCA: Through the temporal window, where the depth is between 40 mm and 65 mm, the direction of blood flow signals in the systolic period is toward the probe. Through the opposite ocular window, where the depth is more than 80 mm, the direction of blood flow signals in the systolic period is away from the probe. When the side window is poorly penetrated, the opposite side of the temporal window can be selected, with a depth of 90 mm or more, and the systolic blood flow direction deviates from the probe. The common carotid artery compression test can confirm MCA, if necessary.

5.2. ICA siphon: Through the ocular window, where the depth is between 60 mm and 70 mm, the direction of the blood flow signal is toward or away from the probe.

5.3. VA: Through the occipital window or the perioccipital window, where the depth is between 55 mm and 80 mm, the direction of the blood flow signal in the systolic period is away from the probe.

5.4. BA: Through the occipital window or perioccipital window, where the depth is between 80 mm and 120 mm, the direction of the blood flow signal in the systolic period is away from the probe.

6. Determination of the results:

6.1. Determination of the vessels: bilateral MCAs are the main judged vessels in the anterior circulation, and the bilateral distal end of the internal carotid artery or the siphon segment of the internal carotid artery is the alternative blood vessel. BA is the main judged vessel in the posterior circulation, and the intracranial segment of the bilateral vertebral artery is an alternative blood vessel.
6.2. Determination of the blood flow frequency spectrum:

(i) Reverberating flow: Both the forward flow signal in systolic period (F) and the reverse flow signal in diastolic period (R) occur in the same cardiac cycle, and the direction of flowing index (DFI) is <0.8. DFI is defined as DFI=1–R/F.

(ii) Small systolic spike in early systole: A single-way forward flow signal in early systolic period, duration is less than 200ms, and velocity is less than 50cm/s.

(iii) Absence of blood flow: Both the forward flow signal in diastolic period (R) and the reverse flow signal in systolic period (F) occur in the same cardiac cycle.

6.3. Determination of frequency: Check twice with an interval of 30 min.

When TCD shows that both the intracranial anterior circulation and the intracranial posterior circulation demonstrate one of the blood flow frequency spectrums mentioned above, the determination of brain death is supported.

7. Pitfalls:

7.1. When both temporal windows are suboptimal, absent, or not accessible (not sufficient to penetrate sound waves), choose the ocular window to detect the contralateral MCA and ipsilateral syphon segment of ICA. When 1 temporal window is poorly penetrated, choose the contralateral temporal window to detect the bilateral MCA and syphon segment of ICA.

7.2. If the blood flow signals are not clear or even are lacking signals through the temporal window the first time, poor penetrability of the temporal window and the artifacts from manipulation should be excluded. The results are for information only, and the determination of brain death should be based on other ancillary tests.

7.3. Occlusive damage of the skull, such as ventricular drainage and cranial decompression, may influence the results. The results are for information only, and the determination of brain death should be based on other confirmatory tests.

7.4. If systolic peripheral arterial pressure is <90 mmHg, blood pressure should be increased before checking TCD.

D. Sequence of ancillary tests

The recommended sequence of the ancillary tests is EEG, SLSEP and TCD. At least 2 tests should fulfill the determination criteria of brain death. If EEG or SLSEP is combined with TCD, the false positive rate will be reduced and the consistency of determination will be improved. If the TCD examination is limited, we can refer to the results of CT angiography (computed tomography angiography, CTA) or digital subtraction angiography (digital subtraction angiography, DSA).

IV. Procedures for determination

The determination of brain death can be considered to consist of 3 steps. First, the clinical evaluation of brain death fulfills the criteria (deep coma, absence of brain stem reflexes, and no spontaneous respiration). Second, at least 2 of 3 ancillary tests fulfill the criteria. Finally, the apnea test confirms apnea. If all the 3 steps mentioned above fulfill the criteria, brain death can be declared.

V. Personnel for determination

At least two physicians participate in the determination of brain death. Furthermore, they should pass standardized training and have at least 5 years of clinical experience.

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