

An Investigation and Suggestions for the Improvement of Brain Death Determination in China

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Abstract

Background: Brain death is the irreversible cessation of the function of the brain including the brainstem. In 2013, the Brain Injury Evaluation Quality Control Centre (BQCC) of the National Health and Family Planning Commission issued criteria and practical guidelines for the determination of brain death. This study aimed to evaluate whether the institutions have adopted these guidelines and to make suggestions for the improvement of the current criteria and practical guidelines for brain death determination in China.

Methods: Consecutive brain death cases from 44 hospitals were evaluated for summary statistics for the following data: the performance of BQCC criteria and practical guidelines, clinical examination, apnea testing, ancillary testing, and the number of examinations as well as the waiting periods between examinations and details of who determined brain death. Data analysis was conducted from January 2013 to December 2017.

Results: A total of 550 cases were obtained. All patients were determined to have deep coma and met the prerequisites for clinical testing. The performance rates of four brainstem reflex examinations (except cough reflex) ranged from 97.5% to 98.0%, and the completion rate as well as the coincidence rate were both 100.0%. The 238 cases (50.7%) completed apnea testing, and 231 cases (42.0%) had to stop apnea testing during the examination because of instability. The performance rates of the three ancillary tests, including electroencephalogram, short-latency somatosensory evoked potential, and transcranial Doppler, were 89.5%, 67.5%, and 79.5%, respectively; furthermore, the coincidence rates were 98.6%, 96.5%, and 99.5%, respectively. The combination of two ancillary tests was more accurate than one single ancillary test. A total of 401 (72.9%) cases successfully underwent two separate examinations to determine brain death with at least a 12-h waiting period. All brain death cases were determined by at least two qualified physicians.

Conclusion: This study might provide suggestions for brain death determination in China.

Key words: Ancillary Tests; Apnea Testing; Brain Death

INTRODUCTION

Since the first Harvard University brain death standard was initially published in 1968, the determination of brain death has been ongoing for half a century. Although there is nearly uniform acceptance of brain death as a concept, there are wide variations regarding prerequisites, methods of testing (including apnea testing), the use and performance of ancillary testing, who determines brain death, and the number of examinations as well as the waiting periods between examinations.^[1-6] These problems have yet to be resolved.

Since the Brain Injury Evaluation Quality Control Centre (BQCC) of National Health and Family Planning Commission issued criteria and practical guidance in 2013 on

the determination of brain death,^[7] brain death determination has progressed in an orderly fashion in China. To ensure that the determination of brain death is performed accurately, physicians who determine brain death is required to undergo certification by the BQCC after training. The purpose of this study was to identify the problems during the period of brain

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death determination and to assess whether the criteria and practical guidelines need to be updated.

METHODS

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University. Waiver of the informed consent requirement was obtained from the Ethics Committee of Xuanwu Hospital, Capital Medical University.

From January 2013 to December 2017, consecutive cases with brain death determination from 44 large three-grade hospitals were obtained through the BQCC database. All cases must meet the prerequisites for brain death determination including deep coma, absence of brainstem reflexes, and no spontaneous respiration. The determination of brain death should fulfill the absence of all the above five brainstem reflexes (pupillary light reflex, corneal reflex, oculocephalogyric reflex, oculovestibular reflex, and cough reflex). If some of the five brainstem reflexes cannot be fully performed, the confirmatory tests should be added. Apnea testing is mandatory to confirm no spontaneous respiration. The determination of brain death should fulfill at least two confirmatory tests.^[7]

Six categories of data were used as follows: (1) the performance criteria and practical guidance for determination of brain death in adults (BQCC version);^[7] (2) details of the clinical examination and apnea testing, including the performance rate, completion rate, and coincidence rate of deep coma, brainstem reflex, and apnea testing; (3) details of ancillary testing including the performance rate, completion rate, and coincidence rate of an electroencephalogram (EEG) showing electrical silence, the short-latency somatosensory evoked potential (SLSEP) of the median nerve showing that bilateral N9 and/or N13 exist, while P14, N18, and N20 are absent, and transcranial Doppler (TCD) sonography showing that the blood flows of the intracranial anterior and posterior circulation demonstrate reverberating flow, small systolic spikes, or the absence of blood-flow signals; (4) the completion rate of repeated examinations (at least twice); (5) the waiting periods between examinations; and (6) the number of physicians who determined brain death.

RESULTS

This study obtained 550 cases from 44 unique hospitals covering 27 provinces in China for the brain death analysis.

Regarding the clinical examination, the performance rate as well as the completion rate of deep coma and the coincidence rate with brain death were all at 100.0%. For brainstem reflex testing, 11 cases did not exhibit a pupillary light reflex as well as oculocephalogyric reflex, 13 cases did not exhibit a corneal reflex, and 14 cases did not perform the oculovestibular reflex. The performance rates of the above four brainstem reflex examinations ranged from 97.5% to 98.0% (536–539 cases), and the completion rate as well as the coincidence rate were both 100% [Table 1].

Eighty-one cases (14.7%) did not undergo apnea testing, mostly because the prerequisites for apnea testing were not satisfied including low blood pressure (16 cases, 19.8%), hypoxemia (25 cases, 30.9%), and refusal of family members (40 cases, 49.4%). Among the remaining 469 cases, 238 cases (50.7%) completed this testing, and all conformed to no spontaneous respiration; 231 cases (49.3%) had to stop apnea testing during the examination because of instability including hypotension (149 cases, 64.5%) and hypoxemia (82 cases, 35.5%).

Due to the limitations of the patient's own pathophysiological conditions or the restriction of the patient relatives' informed consent, approximately 2.0–2.5% of the cases did not undergo brainstem reflex examination, and 49.3% of the cases failed to complete apnea testing [Table 1].

Ancillary testing was mandatorily performed in all cases. Three ancillary tests, including EEG, SLSEP, and TCD, are stipulated in current Chinese guidelines. The performance rate of EEG examinations was 89.5% (492/550), and the coincidence rate of EEG examinations with the brain death standard was 98.6% (485/492 cases). The performance rate as well as the coincidence rate of the SLSEP examination were 67.5% (371/550 cases) and 96.5% (358/371 cases), respectively. Approximately 79.5% (437/550) of patients underwent TCD examination, and the coincidence rate with the brain death standard was 99.5% (435/437 cases). The performance rates of the three ancillary tests ranged from 67.5% to 89.5%, representing EEG, TCD, and SLSEP from high to low. Furthermore, the coincidence rates ranged from 96.5% to 99.5%, representing TCD, EEG,

Table 1: Clinical examination of brain death in the study, n/N (%)

Items	Performance rate	Completion rate	Coincidence rate
Deep coma	550/550 (100.0)	550/550 (100.0)	550/550 (100.0)
Absence of brainstem reflexes			
Pupillary light reflex	539/550 (98.0)	539/539 (100.0)	539/539 (100.0)
Corneal reflex	537/550 (97.6)	537/537 (100.0)	537/537 (100.0)
Oculocephalogyric reflex	539/550 (98.0)	539/539 (100.0)	539/539 (100.0)
Oculovestibular reflex	536/550 (97.5)	536/536 (100.0)	536/536 (100.0)
Cough reflex	550/550 (100.0)	550/550 (100.0)	550/550 (100.0)
Apnea testing	469/550 (85.3)	238/469 (50.7)	238/238 (100.0)

and SLSEP from high to low [Table 2]. The reasons for the failure to perform the ancillary testing were the restrictions of the patient's own conditions such as the interference of narcotic-sedative drugs with the EEG results, the interference of peripheral neuropathy on afferent stimulation with the determination of SLSEP, skull defects that might make the TCD parameters inaccurate, or the subjective choice of the physicians who determined brain death.

The completion rates of both electrophysiology examinations (EEG and SLSEP) were 100.0%, and the coincidence rates were 98.6% and 96.5%, respectively. The performance rate of the combination of the two electrophysiology examinations was 57.6%, and the coincidence rate was 99.4%. The performance rates of the combination of the EEG or SLSEP with TCD were 71.8% and 64.4%, respectively. The coincidence rates of each electrophysiology examinations combined with TCD reached 99.7%. The combination of the two electrophysiology examinations (EEG and SLSEP) and TCD with either EEG or SLSEP was more accurate than any single ancillary testing [Table 2].

Regarding multiple examinations, 401 (72.9%) cases successfully underwent two separate examinations to determine brain death. The results of the two separate examinations were consistent. The main reasons for failing to make the repeated determination were circulatory failure (28.2%, 42/149 cases) and the patient relatives' refusal of treatment and a second brain death determination (71.8%, 107/149 cases). This suggested that not all patients could be evaluated twice. Although the completion rate of the second determination was lower than the first determination, the two results were very consistent (100%). The time required between examinations was stipulated to be at least 12 h in China. Of the 44 hospitals that made repeated examinations, the waiting period between examinations required at least 12 h.

BQCC stipulated the types and the number of physicians who could determine brain death. The data showed that all brain death cases were determined by at least two qualified physicians.

DISCUSSION

There are clear practice differences in the determination of brain death in different countries and regions. The criteria

and practical guidance of the BQCC in 2013 aimed to make the determination of brain death accurate and straightforward in China. This investigation sought to provide evidence for updated practice parameters.

Clinical examination was the first and most important step in all hospitals in which the determination of brain death took place. This study showed that approximately 2.0–2.5% of patients could not undergo brainstem reflex examinations, and only 50.7% of patients successfully completed the apnea testing. Therefore, not all patients could be accurately assessed for brain death according to the results of the clinical examination. The inability to complete the clinical examination and inconclusive apnea testing required the help of ancillary testing.^[1-3] To make more accurate and consistent determinations of brain death in practice, we suggested that ancillary testing should be mandatorily performed in China.

Apnea testing is the core determinant of brain death. This investigation showed that the performance rate of apnea testing was not low (85.3%), however, only 50.7% of cases could be successfully completed. Although this result was higher than that of a single-center study in China (32%),^[8] it was still unsatisfactory. In 2004, one survey, including 129 brain death patients in Argentina, showed that only 50% (65/129 cases) successfully completed apnea testing. The main factors affecting the completion rate were hypotension (12%), acidosis (68%), and hypoxemia (23%).^[9] The Mayo Clinic in the United States reviewed brain death cases from 1996 to 2007 in 2008,^[10] and the results showed that 212 of 228 patients completed apnea testing; only 7% of them were unable to complete the test because of circulatory instability or hypoxemia, and 11.3% of cases had to abort the apnea test process due to hypotension or hypoxemia. The total completion rate of apnea testing was 81.7%. Thus, the performance of apnea testing might be a common problem worldwide. We suggested that when the patient did not meet the prerequisites to perform apnea testing or had to abort apnea testing, the ancillary tests must be performed; brain death can be determined only when the ancillary tests meet the criteria for determining brain death. In addition, we suggested that the focus of clinical determination of brain death should be focused on the optimization and technological improvement of apnea testing in order to better maintain life and organ functions and improve the performance and completion rates of apnea testing.^[7]

The popularity of common ancillary tests, including EEG, SLSEP, and TCD, has significantly improved since 2013 with the help of the BQCC's training program. This investigation showed that all hospitals were equipped with the instruments required for ancillary testing. The performance, completion, accuracy, and combination of the three ancillary tests were good. The results confirmed that the current three ancillary tests (EEG, SLSEP, and TCD) were feasible and reliable for determining brain death in China.

Regarding ancillary testing, it is still controversial worldwide. The American Neurology Association (ANN) guidelines for

Table 2: Ancillary tests for the determination of brain death in this study, n/N (%)

Items	Performance rate	Completion rate	Coincidence rate
EEG	492/550 (89.5)	492/492 (100.0)	485/492 (98.6)
SLSEP	371/550 (67.5)	371/371 (100.0)	358/371 (96.5)
TCD	437/550 (79.5)	437/437 (100.0)	435/437 (99.5)
EEG and SLSEP	317/550 (57.6)	317/317 (100.0)	315/317 (99.4)
EEG and TCD	395/550 (71.8)	395/395 (100.0)	394/395 (99.7)
SEP and TCD	354/550 (64.4)	354/354 (100.0)	353/354 (99.7)

EEG: Electroencephalogram; SLSEP: Short-latency somatosensory evoked potential; TCD: Transcranial Doppler.

the determination of brain death in adults indicated that brain death was a clinical diagnosis, and confirmatory testing was not mandatory but was recommended in those patients, for example, the clinical testing could not be reliably performed or evaluated, toxic drug levels, inconclusive apnea testing, and sleep apnea or severe pulmonary disease resulting in the chronic retention of CO₂. Although confirmatory tests were not required, the clinical application of the common confirmatory tests included angiography, radionuclide scintigraphy, EEG, TCD, somatosensory evoked potentials, and atropine challenge.^[11] In 2015, a global survey including 91 countries showed that EEG was the mandatory ancillary test in 28% of countries as well as recommended as an ancillary test in 47% of countries, and TCD was mandatory in 5% of countries as well as recommended in 53% of countries to determine brain death.^[2] In 1999, a European survey showed that most countries recommended EEG (except Denmark), half of the countries performed the SEP test, and few countries (Germany and Austria) adopted the TCD test.^[12] The EEG, SEP, and TCD are still the main ancillary tests for brain death determination with high selectivity, although controversy exists among different countries. Therefore, the BQCC still recommends that EEG and SLSEP should be performed as electrophysiological tests to determine brain death, and TCD should be performed as a technique for the detection of cerebral blood flow for brain death determination. There are two tests for electrophysiological examination (EEG or SLSEP); however, TCD is the only test for cerebral blood flow. Therefore, it is necessary to carry out new ancillary testing to determine brain death in China such as computed tomography angiography (CTA). When the TCD examination is limited, other cerebral blood flow examinations might be an alternative.

There are no mandatory stipulations on the number of ancillary tests to determine brain death in most countries.^[4,5,13] Our previous study showed that the false-positive rates of EEG, SLSEP, and TCD were 3%, 22%, and 25%, respectively.^[8] The accuracy rate of any one test for brain death determination had not reached 100%. Therefore, it is stipulated that the combination of any two accuracy tests is mandatory. In this study, the combination of two electrophysiological examinations (EEG and SLSEP) or one electrophysiological examination with TCD could improve the accuracy rate to 99.4–99.7%. Therefore, we suggested that the criteria regarding the number of ancillary tests for the determination of brain death should be retained. The physicians, who determine brain death, have the right to choose the combination of three examinations as ancillary testing to ensure accuracy.

The stipulations of multiple examinations and waiting periods are also different worldwide. The results of this study showed that 72.9% of cases successfully completed repeated examinations for the determination of brain death. The results of the two separate examinations were fully consistent. One of the main reasons for the failure to make the second examination was circulatory failure, which would lead to a

loss of time for determination. The longer the waiting period, the more opportunity is lost. According to our investigation, many relatives abandoned treatment and refused to repeat the determination. The time required between examinations was stipulated to be at least 12 h in China. Although the ANN guidelines recommend a repeat clinical evaluation 6 h later, this interval is arbitrary.^[11] In 2006–2008, a study performed among the top 50 neuroscience institutions in the United States found that 71% of hospitals required multiple examinations and 3% required more than two, and the time required between examinations varied widely, from 1 to 24 h. The most commonly stipulated waiting period was 6 h, however, this interval could be shortened if there was supportive ancillary testing or lengthened for children, for patients with brain death of unknown cause, or for patients with a nonstructural cause.^[1] In 2016, an analysis of brain death in a district hospital provided by an organ access organization in the United States (covering 492 hospitals in 50 states) showed that 65.9% (324/492) of hospitals required two examinations and 20.9% (103/492) of hospitals required more than two examinations (the highest 5); only 13% (64/492) of the hospitals required only one examination. Furthermore, 54.1% (266/492) of hospitals controlled the time between the examinations, of which 71.1% (189/266) stipulated the waiting period as at least 6 h, 2.6% (7/266) stipulated at least 12 h, 1.1% (3/266) stipulated at least 24 h, and only 10.2% (27/266) repeated the examination in less than 6 h.^[14]

The results of the European survey showed that some countries, such as the UK, Denmark, Italy, Poland, Switzerland, Germany, and Austria, required repeat examinations (clinical determination, clinical joint ancillary test, and ancillary test), and the waiting period ranged from 2 to 12 h. Other countries, such as France, Holland, Belgium, Luxembourg, and Finland, did not require repeat examinations.^[12]

According to the results of this study, the following suggestions were provided: if the clinical determination (including apnea testing) and two ancillary tests all fulfill the criteria of brain death, a repeat examination is not mandatory; if the clinical determination is not complete, an increased number of confirmatory tests and repeat examinations should be performed 6 h after the first examination, and there should be at least one apnea test to confirm a lack of spontaneous respiration.

The criteria and practical guidelines for the determination of brain death in adults (BQCC version) were published 5 years ago. There may be new insights or new problems in brain death determination. This investigation provided details on the assessment practices in China. We hope that this investigation will provide evidence to update the BQCC guidelines. The BQCC will continue to take steps to ensure that the determination of brain death is more accurate and consistent in China.

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Conflicts of interest

There are no conflicts of interest.

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中国脑死亡判定调查与改进建议

摘要

背景：脑死亡是大脑功能的不可逆转的停止，包括脑干。2013年，国家卫生和计划生育委员会脑损伤评估质量控制中心（BQCC）发布了确定脑死亡的标准和实用指南。本研究旨在评估机构是否已采纳这些指导方针，并为改进我国现行的脑死亡判定标准和实用指导方针提出建议。

方法：对44家医院连续发生的脑死亡病例进行总结性统计，包括BQCC标准和实用指南的执行情况、临床检查、呼吸暂停试验、辅助检查、检查次数以及检查之间的等待时间。世卫组织确定脑死亡的检查和细节。资料分析于2013年1月至2017年12月进行。

结果：共获得550例患者。所有患者均确诊为深昏迷，符合临床试验的先决条件。脑干反射检查（除咳嗽反射外）完成率97.5–98.0%，符合率100.0%。约238例（50.7%）患者完成呼吸暂停试验，231例（42.0%）患者因检查不稳定而不得不停止呼吸暂停试验。脑电图（EEG）、短潜伏期体感诱发电位（SLSEP）、经颅多普勒（TCD）三项辅助检查的检出率分别为89.5%、67.5%和79.5%，符合率分别为98.6%、96.5%和99.5%。两个辅助测试的组合比一个单一的辅助测试更准确。总共有401例（72.9%）患者在至少12小时的等待期内成功地进行了两次独立的检查以确定脑死亡。所有脑死亡病例由至少两名合格的医师确定。

结论：本研究为中国脑死亡测定指南的更新和完善提供了依据。