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Diagnosis of Brain Death in a Multidisciplinary Hospital

Alexey I. Gritsan[1,2]*, Nikolay Y. Dovbysh[1,2], Egor E. Korchagin[2]

[1] Prof. V.F. Voino-Yasenetsky Krasnoyarsk State Medical University, Ministry of Health of Russia,
1 Partizana Zheleznyaka Str., 660022 Krasnoyarsk, Krasnoyarsk area, Russia
[2] Regional Clinical Hospital,
3A Partizana Zheleznyaka Str., 660022 Krasnoyarsk, Russia

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***Correspondence to:** Alexey I. Gritsan, gritsan67@mail.ru

Summary

Brain death diagnosis (BDD) remains a challenge for anesthesiologists and intensive care physicians despite existing regulatory frameworks.

Objective. To evaluate the frequency of BDD procedure and identify factors limiting its implementation in a multidisciplinary hospital setting.

Materials and Methods. A single-center retrospective study was conducted including 698 patients by total sampling. Of these, 98 (14%) had brain injury and were selected for further analysis. From this cohort, patients who died within 15 days of hospital admission ($N = 61$) were identified. A subgroup of patients with a Glasgow Coma Scale (GCS) score of 3–5 was then selected ($N = 38$). For comparison, a literature search was performed in PubMed using the query «brain death criteria» and in eLibrary.ru using the keywords «brain death diagnosis».

Results. BDD was initiated in 12 (31.6%) cases within the GCS 3–5 subgroup, with brain death confirmed in 8 (21.1%) patients, including 5 (63%) women and 3 (37%) men. Complete BDD procedures were performed in 6 (75%) patients with non-traumatic intracerebral hemorrhage (ICH), 1 with non-traumatic subarachnoid hemorrhageь (SAH), and 1 with traumatic brain injury (TBI) (12.5% each). The median patient age was 59 [43; 65] years, the median GCS score was 3 [3; 3], and the median FOUR score was 0 [0; 0]. Median hospital length of stay was 1.5 [1; 2.5] days, and median intensive care unit (ICU) stay was 1 [1; 2] day.

Conclusion. Insufficient pupil diameter (5 mm) is a limiting factor for the performance of BDD procedures in grade III coma patients.

Keywords: brain death diagnosis; transplantation

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Advances in medical care have led to an increase in the number of patients receiving intensive therapy despite irreversible brain damage of primary or secondary origin. For anesthesiologists and intensivists, the timely diagnosis of death based on neurological criteria is critical. This practice helps to discontinue futile intensive care and prevents the emotional burden on health care professionals who recognize the unfavorable prognosis but continue to provide care [1].

Failure to diagnose brain death results in the loss of potential organ donors who meet neurological criteria, depriving patients awaiting transplantation of a chance at life. It is estimated that the annual need for kidney transplants is approximately 40 cases per million population, while the need for heart and liver transplants is 20 cases each. Consequently, the annual need for kidney transplants in the population is about 4,000–5,000, and for liver and heart transplants, 1,500–2,000 each. Patients in need of organ transplantation are treated in specialized centers, where the mortality rate of patients on the waiting list ranges from 10% to 35% [2].

The aim of the study was to evaluate the frequency of brain death determination by intensivists and to identify factors limiting its implementation in a multidisciplinary hospital.

Materials and Methods

We conducted a single-center retrospective study that included a comprehensive sample of 698 patients who died between September 4, 2023, and March 22, 2024 (201 days). The study focused on seven anesthesiology and intensive care units (112 beds) within a large multidisciplinary hospital with a catchment population of approximately 300,000 people. The hospital includes a vascular center and performs neurosurgical procedures for neuro-oncological and cerebrovascular conditions.

Of the total patient sample, 98 cases (14%) involved brain damage and were selected for further analysis (see Figure). The types of brain injury are detailed in Table 1.

From the cohort of selected patients, a group of patients who died within 15 days of hospital admission was identified (*N*=61; see Figure and Table 1). This group was selected because in patients with a hospital stay longer than 15 days, the cause of death was primarily progression of the organ failure syndrome secondary to infectious complications.

In the next step, a subgroup consisting of patients with an ICU stay of 0–15 days and a reduced level of consciousness scoring 3–5 on the Glasgow Coma Scale (GCS) was identified from this group (subgroup, *N*=38).

The study cohort had 48 women (49%) and 50 men (51%). The study group included 32 women (52%) and 29 men (48%), while the subgroup consisted of 17 women (45%) and 21 men (55%).

Decisions on the determination of brain death (DBD) were made in accordance with the Order of the Ministry of Health of the Russian Federation dated December 25, 2014, No. 908n, «On the Procedure for Determining Human Brain Death» [3]. The biochemical criteria required to initiate the DBD procedure included pH 7.35–7.45, sodium 135–145 mmol/L, potassium 3.5–5.0 mmol/L, blood glucose 3.0–8.3 mmol/L, and magnesium and calcium concentrations within their reference ranges, excluding brain death due to their abnormal levels [4].

We evaluated the length of hospital stay, time spent in the intensive care unit (ICU), duration of mechanical ventilation, patient age, and level of consciousness on admission to the ICU using the Glasgow Coma Scale (GCS) and the Full Outline of UnResponsiveness (FOUR) scale.

To compare our results with published data, a literature search was performed in the PubMed database using the query «brain death criteria» and in the eLibrary.ru system using the query «констатация смерти мозга» («determination of brain death»). A total of 5,939 sources were identified, covering the period from 1968 to 2024. Full-text publications from 2014 to 2024 were selected for detailed analysis.

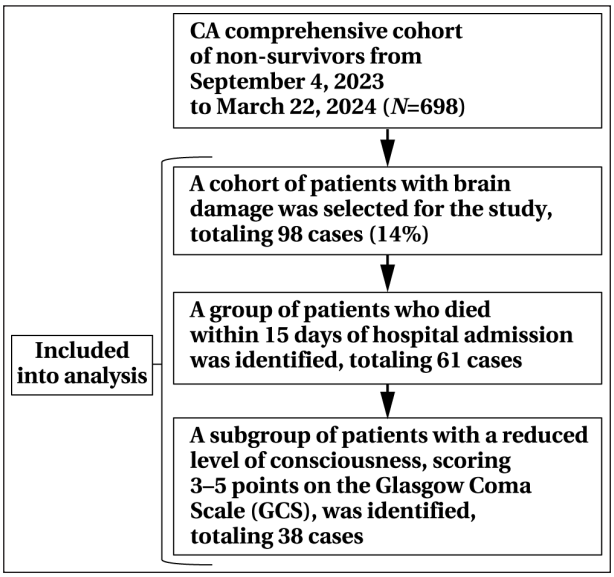

Fig. Study flowchart.

The collected data were processed using IBM SPSS Statistics 22 for Windows (SPSS, Chicago, Illinois) and Microsoft Office Excel 2013. Shapiro–Wilk test was used to determine the normality of data distribution. Quantitative data are presented as median *(Me)* and interquartile range *(Q1; Q3)*.

Results

Patient characteristics, length of hospital stay, length of ICU stay, and duration of mechanical ventilation are summarized in Table 2.

In the subset of patients, determination of brain death (DBD) was initiated in 12 cases (31.6%). Brain death was confirmed in 8 patients (21.1%), including 5 females (63%) and 3 males (37%).

Table 1. Distribution of patients by diagnosis, *N* (%)

Diagnosis	Participants		
	Entire cohort (*N* = 98)	Group (*N* = 61)	Subgroup (*N* = 38)
Ischemic stroke	35 (35.7)	18 (29.5)	9 (23.7)
Intracerebral nontraumatic hemorrhage	27 (27.6)	19 (31.1)	14 (36.8)
Subarachnoid hemorrhage	7 (7.1)	6 (9.8)	4 (10.5)
Traumatic brain injury	15 (15.3)	9 (14.8)	9 (23.7)
Brain tumor (primary or metastatic, operated or not operated)	10 (10.2)	5 (8.2)	0
Secondary meningoencephalitis	1 (1.0)	1 (1.6)	1 (2.6)
Cardiopulmonary resuscitation (secondary brain damage)	3 (3.1)	3 (4.9)	1 (2.6)

Table 2. Characteristics of included patients, *Me* [*Q1*; *Q3*].

Parameter	Participants		
	Entire cohort (*N* = 98)	Group (*N* = 61)	Subgroup (*N* = 38)
Age, years	67 [55; 76]	64 [50; 70]	61 [47; 68]
GCS, points	6 [3; 9]	3 [3; 6]	3 [3; 3]
FOUR, points	6 [0; 16]	0 [0; 16]	0 [0; 0]
Length of stay in hospital, days	9 [3; 27]	4 [3; 8]	3 [2; 6.7]
Length of stay in ICU, days	5 [2; 11]	4 [2; 7]	3 [2; 5.5]
Duration of lung ventilation, days	4 [1; 10]	3 [1; 6]	3 [2; 6]

Complete DBD was performed in 6 patients with intracerebral hemorrhage (75%), 1 with subarachnoid hemorrhage (12.5%), and 1 with traumatic brain injury (12.5%). The median age of these patients was 59 years [43; 65]. The Glasgow Coma Scale (GCS) score was 3 [3; 3] and the Full Outline of UnResponsiveness (FOUR) score was 0 [0; 0]. The median length of hospital stay was 1.5 days [1; 2.5], and ICU stay was 1 day [1; 2].

DBD was discontinued in four cases for the following reasons:

— Patient P. V. I., male, age 65 years, with the diagnosis of intracerebral hemorrhage and community-acquired pneumonia complicated by severe acute respiratory distress syndrome ($PaO_2/FiO_2 < 100$ mmHg). Apnea oxygenation testing was not initiated.

— Patient Z. R. S., male, age 24 years, with the diagnosis of TBI with ruptured tympanic membrane. EEG recording was not possible due to inability to apply electrodes.

— Patient K. M. V., a 55-year-old male with a diagnosis of intracerebral hemorrhage, developed hemodynamic instability during the apnea-oxygenation test, leading to termination of the test. Death occurred 30 minutes later.

— Patient Z. T. V., female, age 66, diagnosed with ischemic stroke with type 4 hemorrhagic transformation (intracerebral hematoma), developed hemodynamic instability during the apnea-oxygenation test. Death occurred 12 hours later.

DBD could not be initiated in 26 patients for various reasons:

— 19 (50.0%) patients had a pupil diameter less than 5 mm, of them 2 patients had pupil diameter less than 5 mm, preserved photoreaction and preserved breathing pattern, 4 patients had pupil less than 5 mm and preserved breathing pattern, and 13 patients had only diameter less than 5 mm;

— in 1 patient (2.6%) diazepam was administered during emergency medical care, and the length of hospital stay was less than 3 days;

— 5 (15.8%) patients with out-of-hospital/nosocomial pneumonia developed septic shock;

— 1 (2.6%) patient developed hypotension that was not corrected by 2 sympathomimetics after CPR.

After DBD in 8 potential organ donors, organ procurement was performed in 6. Organ procurement was not performed for a 44-year-old patient admitted with ICH who had previously undergone surgery for breast cancer, and an 88-year-old patient with ICH.

Discussion

According to the findings of The World Brain Death Project, the minimum criteria for diagnosing brain death include the presence of coma, absence of brainstem reflexes, and apnea. Assessment of cerebral blood flow and electroencephalography (EEG) should be used if the clinical examination does not provide sufficient information [5].

It is important to note that these criteria for determining brain death are fully described in the Russian Ministry of Health Order No. 908n of December 25, 2014, «On the Procedure for Determining Human Brain Death» [3]. In addition, the criteria specified in this order are reflected in the diagnostic algorithm for brain death proposed by M. Piradov and E. Gnedovskaya in 2010 [6], which remains a practical and informative tool.

There are significant differences in brain death criteria around the world, as demonstrated by the comprehensive study by A. Lewis et al. that analyzed data from 136 countries [7]. The study found that 83 countries have established brain death determination protocols; however, 78 of these have unique characteristics, and 53 countries have no such protocols at all.

Clinical signs that are evaluated in confirming brain death include the following:

— Pupil response to light: assessed in 70 (90%) countries.

— Corneal reflex: assessed in 68 (87%) countries.

— Oculovestibular reflex: assessed in 67 (86%) countries.

— Gag reflex: assessed in 64 (82%) countries.

— Cough reflex: assessed in 62 (79%) countries.

— Oculocephalic reflex: assessed in 58 (74%) countries.

— Cranial trigger point pain stimulation: assessed in 37 (47%) countries.

— Pain stimulation in extremities: assessed in 22 (28%) countries.

— Assessment of other reflexes: in 22 (28%) countries.

The apnea oxygenation test (AOT) is included in 91% of brain death protocols worldwide. However, there is variability in both the methodology of its performance and the target arterial carbon dioxide tension ($PaCO_2$) levels required. Ancillary tests to confirm brain death are required in 22% of protocols.

An interesting comparison of the frequency of diagnosis of brain death using national protocol criteria versus American or Chinese criteria was presented in a study by clinicians from Beijing Tiantan Hospital, which examined 37 patients with primary brain injury [8].

In the protocol used in China, confirmation of brain death requires the use of at least two of three ancillary tests: transcranial Doppler ultrasonography (TCD), electroencephalography (EEG), or somatosensory evoked potentials (SEP). AOT is mandatory and serves as the final step in the determination process. The interval between the first

confirmatory step and repeat ancillary testing is 12 hours.

In the United States, ancillary tests are used only when the clinical examination or apnea test cannot be performed due to special circumstances.

According to the Chinese national protocol, brain death was diagnosed in 9 of 37 potential organ donors, while according to the US criteria, brain death was diagnosed in 33 of the same group. Notably, intracranial infection leading to Grade III coma (with absence of brainstem reflexes) is not a reason for «non-inclusion» into brain death protocol under the Chinese recommendations on DBD.

These findings highlight significant differences in national guidelines on DBD, which may affect the frequency of brain death diagnoses.

The primary cause of brain death in our study was acute cerebrovascular event (ACVE), which accounted for 10 of 12 (83.3%) cases in which the brain death protocol was initiated and 7 of 8 (87.5%) cases in which it was successfully completed.

A decreasing proportion of traumatic brain injuries (TBI) among potential organ donors after determination of brain death has been observed in most European and North American countries. This trend has been attributed to improved vehicle safety, advances in traffic management, and a reduction in traffic accidents [9–11].

In our study, among potential donors diagnosed with brain death due to ACVE, intracerebral hemorrhage (ICH) was the leading cause, accounting for 75% of cases. ICH was present in 66.6% of brain death protocol initiations. The predominance of ICH as a cause of brain death has also been reported by other investigators. For example, D. Escuderoa et al. [10] and A. Sanchez-Vallejo et al. [12] identified ICH as the cause of brain death in 49% of cases.

Several studies have documented a temporal decrease in subarachnoid hemorrhage (SAH) as a cause of brain death. This trend has been attributed to improvements in the management and treatment of patients with SAH [13].

In our study, only one patient in whom the DBD protocol was initiated but not completed presented with ischemic stroke (IS) as the underlying cause of brain death, although this case also involved a type IV hemorrhagic transformation.

The low number of patients with IS progressing to brain death may be due to the presence of «reserve spaces» in the elderly population. In these cases, the development of a large cerebral infarct does not always lead to transtentorial herniation, despite the displacement syndrome. An important factor in reducing mortality in patients with IS is the widespread use of decompressive craniectomy to treat life-threatening cerebral edema [11].

The median age of potential donors undergoing DBD procedure in our study was 59 years, which is consistent with previously reported findings of 60.7 years [8, 9]. In Switzerland, P. Grzonka et al. reported a mean age of 57 years for brain-dead individuals [13]. However, younger donor ages have been documented; for example, A. Seifi et al. found a mean age of 47.83 ± 20.93 years [14], and M. Sahin et al. reported a mean age of 43 years [15] among potential donors. The researchers attributed this lower age to the relatively younger population in Turkey compared to Europe [14, 15].

According to M. Minina [16], the median age of brain-dead donors in Moscow between 2009 and 2013 was approximately 40 years.

In our study, the median time from admission to the intensive care unit to initiation of DBD was 1.5 days, and the median duration of mechanical ventilation was 1 day.

According to the literature, the time from hospital admission to determination of brain death varies significantly between countries. In Turkey, 69.69% of DBD procedures are performed in patients who stay in the ICU up to 7 days, 22.17% in those who stay 7–14 days, and 8.14% in those who stay longer than 14 days [17]. D. Escuderoa et al. report that when the DBD protocol is initiated within the first 24 hours of admission, brain death is diagnosed in 48% of cases in hospitals with neurosurgical services and in 59% of cases in hospitals without such services [10].

A major factor preventing DBD in 13 patients in our study was a pupil diameter of less than 5 mm. These patients also showed absence of light reflex, response to painful stimuli, spontaneous breathing patterns (making apneic oxygenation testing impossible), and oculocephalic and oculovestibular reflexes.

A retrospective study by P. Lenga et al. [17] of 17 potential donors over 18 years of age with confirmed brain death reported a mean age of 57.3 years. Using the NPi®-200 pupillometer (Neuroptics, Laguna Hill, USA), the mean right pupil diameter was 4.9±1.3) mm and the mean left pupil diameter was 5.2±1.2) mm. In countries such as Australia, New Zealand and Japan, a pupil diameter of less than 4 mm is a prohibitive factor for initiating DBD protocols [19].

In the study by D. Shlugman et al. [19], some of the 148 potential organ donors with a confirmed diagnosis of BD had pupils less than 4 mm in diameter. Similarly, A. Khandelwal et al. [18] described several challenging cases of patients with pupils less than 3 mm in diameter. However, after careful evaluation of the brainstem reflexes, the DBD protocols were successfully performed in these cases.

In our study, three brain death determinations (25%) were terminated due to the inability to perform

AOT. Of these, two cases (16.6%) were related to hemodynamic instability during the test, and one case (8.4%) was due to the inability to maintain the target gas exchange parameters specified in Russian Ministry of Health Order No. 908n due to the development of acute respiratory distress syndrome (ARDS). All three patients died soon after.

The incidence of symptomatic arterial hypotension during AOT was 9% (8 of 94 patients) in the study by X. L. Wu et al. [20]. The authors attributed this to inadequate preoxygenation prior to testing. A previous study by J. L. Goudreau et al. [21] reported arterial hypotension in 24% of 145 AOT cases. In both studies, patients had PaO_2 values greater than 200 mmHg, but target blood pressure was maintained with vasopressor infusions.

Neurogenic lung injury associated with severe brain injury occurs in 2% to 42.9% of cases according to various authors [22, 23] and often prevents the achievement of target oxygenation levels. I. Stulin et al. reported that maintaining the required blood gas parameters was not possible in 11% of cases, making the DBD protocol impossible [24].

In one case, the DBD protocol was not performed in a patient with TBI because it was not possible to place electrodes for electroencephalography (EEG) due to significant cranial bone deformities and ruptured tympanic membranes, which also precluded performance of the oculovestibular reflex test. A literature search of PubMed and eLibrary did not reveal any similar cases of DBD failure due to such factors in patients with TBI [25], suggesting that this is an extremely rare cause of protocol noncompliance.

The incidence of DBD varies considerably between countries and even between regions within the same country. In Spain, regional rates range from 55 to 25 protocols per 1 million population [10]. Time trends also play a role; in the United States, the number of confirmed cases of brain death increased from 12,575 in 2012 to 15,405 in 2016 [5].

In Moscow, according to I. D. Stulin et al. [24], mobile neurodiagnostic teams confirmed brain death in more than 500 cases between 1995 and 2010, including 282 cases between 2007 and 2010. In addition, M. Minina [16] reported that from 2011 to 2013, 243 effective donors were recorded after DBD procedure in Moscow.

The study of I. Voznyuk et al. [26] presented data on the application of the protocol of DBD at the St. Petersburg Research Institute of Emergency Medicine named after I. I. Dzhanelidze. Between 2014 and 2019, 48 DBD protocols were initiated in 313 patients with grade III coma, representing 15.3% of cases.

The proportion of completed DBD protocols among initiated cases (8 out of 12) in our study is consistent with reported data from Russia.

Study limitations. This study did not consider the presence of comorbidities or associated conditions, which limits the generalizability of the results.

Conclusion

The primary factor limiting performance of the procedure of brain death determination was a pupil diameter of less than 5 mm in patients with grade III coma.

The leading cause of brain death were cerebral vascular conditions, particularly intracerebral hemorrhage.

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