Original Article

BRAIN DEATH

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Abstract

Background
Brain death is defined as the complete and irreversible loss of brain and brainstem function, although other organ systems in the body may continue to function. Following the onset of brain death, brainstem reflexes are lost sequentially in a craniocaudal direction.
Aim
This investigation aimed to compare clinical diagnostic criteria—specifically brainstem reflexes, such as the pupillary response to light, the corneal reflex, and motor responses to pain stimulation—with the instrumental confirmatory test for brain death using cerebral angiography.
Materials and Methods
A group of 30 patients who underwent cerebral angiography to confirm brain death was reviewed. Early clinical tests indicating brain death were compared with the final confirmatory tests using cerebral catheter angiography in the same patient population.
Results
The initial clinical tests indicating brain death corresponded with the final instrumental confirmatory tests in all patients.
Conclusion
Neurological tests assessing motor responses to painful stimuli, the corneal reflex, and the pupillary light response proved to be as reliable for diagnosing brain death as cerebral angiography.

Keywords: brain, brain stem, death, reflex, brain angiography

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Introduction

The term *brain death* refers to the irreversible cessation of all brain functions, including those of the cerebral hemispheres and brainstem. From a legal standpoint, brain death is recognized as the definitive death of a person.[1] The term *whole brain death* has been introduced to describe the complete loss of functions in both the cerebral hemispheres and the brainstem.[2]

From a neurobiological perspective, the death of a human being is not a sudden or instantaneous event. Death is considered a process that ultimately leads to the irreversible cessation of organ function over time. Continued cardiac activity after brain death does not affect the diagnosis of death. It is well-known that cardiac arrest can be reversible; with resuscitation measures, it is often possible to restart the heartbeat. However, the cessation of brain function is a definitive event. In other words, once brain death is diagnosed, it is not possible to restore brain activity.[3]

The onset of irreversible failure of central nervous system functions consequently leads to the gradual weakening of cardiac and respiratory functions. This process is referred to as the *death process*.[4] The duration of this process represents the time window during which organ donation is possible.[5] Thanks to medical support techniques applied in intensive care units, the cessation of cardiac function can be delayed for hours or even days.

Pathophysiology of Brain Death

The ultimate mechanism underlying brain death is an increase in intracranial pressure (ICP) above the mean arterial blood pressure, resulting in the cessation of blood flow to brain tissue. Common causes of this pathophysiological mechanism include head injuries, brain injuries, and spontaneous intracranial hemorrhages, all of which can cause brain edema and elevate intracranial pressure. Once intracranial hypertension reaches a critical level, brain blood flow ceases, leading to brain death.[5]

The primary goal in treating such patients is to implement measures to reduce intracranial pressure. Surgical procedures aimed at lowering intracranial pressure, known as decompressive surgeries, are considered life-saving interventions.[6] It is estimated that approximately 5–10% of all patients admitted to intensive care units (ICUs) eventually progress to brain death.[7]

Diagnosis of Brain Death

Three clinical signs are considered crucial for diagnosing brain death: coma, absence of brainstem reflexes, and apnea (cessation of respiratory movements). Before initiating the diagnostic assessment, it is essential to rule out conditions such as hypothermia and metabolic encephalopathy, which can clinically mimic brain death.[3]

The brainstem contains vital centers responsible for regulating the body's automatic functions, including the respiratory center, cardiac center, cough reflex center, swallowing center, and blood pressure center (Fig. 1).

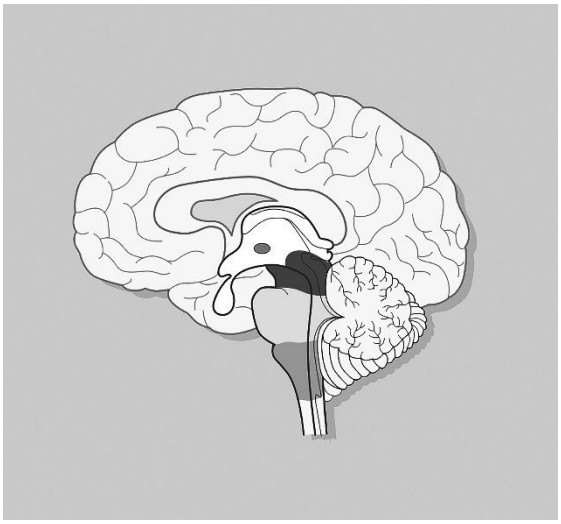

Fig. 1 The brain stem

The pathophysiology of brain death ultimately leads to cessation of respiration, followed by asystolic cardiac arrest due to hypoxemia. The most cranial center in the brainstem controls the pupillary response to light, and thus, a delayed response to light is typically the first sign in the progression toward brain death. This is followed by full dilation of the pupils without light response and absence of the corneal reflex. Finally, the process results in apnea, as the respiratory center is in the most caudal part of the brainstem, the medulla oblongata.[5]

The aim of this investigation was to compare clinical diagnostic criteria—comprising three simple neurological tests—with the instrumental confirmatory test of brain death.

The Tests for Brain Death

1. Pupillary response to light
2. Corneal reflex
3. Motor response to pain stimulation

These clinical tests were compared with the instrumental confirmatory test for brain death, which was:

Brain catheter angiography

Given that the first clinical signs of brain death are lack of reaction to painful stimuli, pupillary dilation, and absence of the corneal reflex, this study aimed to correlate these indicators with the confirmatory findings of cerebral angiography in the same patient population. Cerebral angiography is considered the gold standard for diagnosing brain death, as the absence of intracerebral blood flow demonstrated through this test is regarded as an absolute confirmatory sign of brain death.[8–10]

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The question addressed was whether the clinical neurological tests were reliable and how confident these tests were compared to the absolute confirmatory instrumental test, cerebral angiography. The three neurological tests are simple and suitable for bedside assessment of brainstem function.

The first test involves examining the size and shape of the pupils and their response to direct light, also known as the photomotor reflex. In this context, dilated pupils that do not react or change size when exposed to strong direct light are consistent with the diagnosis of brain death.[11]

The second test, also a straightforward bedside test, is the corneal reflex response.[12] (Fig. 2) The corneal reflex refers to the contraction of the orbital and eyelid muscles in response to a light touch on the cornea, typically using a cotton swab.

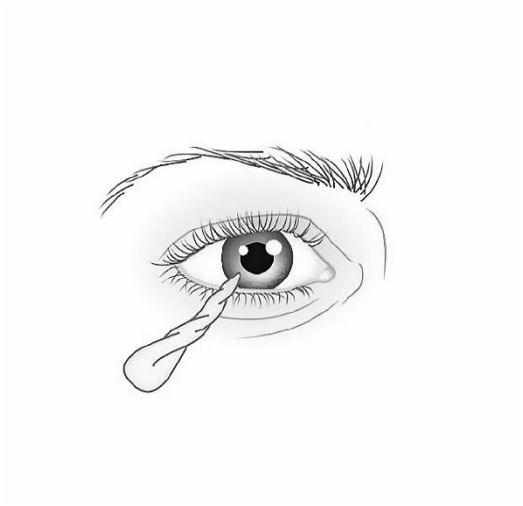

Figure 2. The corneal reflex

Thus, tactile stimulation elicits a vital response, typically a prompt blinking or movement of the eyelid and orbital muscles. However, the absence of this response is consistent with brain death.[12] The third test involves painful stimulation, which would normally provoke movement of the face and/or extremities. Pain stimuli, such as squeezing the skin or applying pressure to the orbital rim, are used to observe any muscle movements in response to intense pain. The absence of movement following painful stimuli is also consistent with brain death.[13]

In this group of patients, angiography was performed at least 6 hours after the initial clinical diagnosis of brain death. This timing adhered to the formal regulations of the national organ transplant program, which mandates that clinical assessments be conducted three times over a 6-hour period before proceeding with the instrumental confirmatory test.[14]

The aim of our investigation was to compare the initial bedside clinical diagnosis of brain death with the definitive confirmation of death through cerebral angiography.

Material and Methods

The clinical records of 30 patients who underwent cerebral angiography for confirmation of brain death were reviewed. These patients met the criteria for the national organ transplant program. Cerebral angiography was the final instrumental test used to confirm brain death in this group of patients, who were selected as candidates for the national organ donation program at the Clinical Hospital Centre Zemun, between December 2010 and June 2019.

Neurological follow-up and reflex assessments were conducted by the hospital's Brain Death Team. The team consisted of three members: a neurologist, a neurosurgeon, and an anesthesiologist. The diagnostic protocol included cerebral catheter angiography performed via the transfemoral route.

Results

The patients' ages ranged from 17 to 69 years, with a mean age of 53 years. There were 18 females (60%) and 12 males (40%). The underlying medical conditions were as follows: hemorrhage due to rupture of a brain aneurysm in 12 patients (40%), head and brain trauma in 8 patients (27%), spontaneous intracerebral hemorrhage in 6 patients (20%), massive cerebral ischemia in 3 patients (10%), and malignant brain edema following benign brain tumor surgery in 1 patient (3%).

Overall, vascular pathology was the underlying cause of brain death in 21 patients (70%). The initial clinical tests, including assessments of motor response, corneal reflex, and pupillary response, indicated brain death in all patients. The cerebral angiography, as an instrumental test, confirmed brain death in every patient. The typical scan, showing the absence of

the intracerebral blood flow network—referred to as the "Empty Skull" sign—was observed in each case (Fig. 2).

Fig. 2 Cerebral angiography in brain death shows an absence of the vascular network in the brain, known as the "Empty Skull" sign. Vascular flow is halted at the base of the skull (arrow).

Thus, the initial clinical bedside testing aligned with the final instrumental confirmation in all patients. Our diagnostic criteria, both neurological and instrumental, demonstrated 100% sensitivity, 100% specificity, and a 100% positive predictive value for all 30 patients included in the study.

Discussion

Different approaches to brain death criteria have been recognized in national legislation across various countries.[15] A worldwide study on brain death protocols in 136 countries revealed considerable variability in how brain death is determined. The most used tests were the pupillary reflex (87%) and corneal reflex (86%).[16]

The brainstem reflexes, which are integrated within the neuronal circuits of the brainstem, indicate the vitality of the brainstem itself, comprising the medulla oblongata, pons, and mesencephalon (Fig. 1). Our review confirmed that the absence of motor, corneal, and pupillary responses indicated the onset of brain death in each of the 30 patients. The diagnostic protocol proceeded with cerebral catheter angiography, which revealed the "Empty Skull" sign—i.e., the absence of the intracerebral vascular network (Fig. 2). [9]

While computed tomography angiography (CTA) is a noninvasive and widely available technique for determining cerebral blood flow, it is not recommended for routine use in brain death confirmation. This is because CTA may show signal enhancement in the vessels at the base of the skull, which can mimic blood flow. As such, CTA is not considered the method of choice for diagnosing brain death.[17],[18]

Cerebral pan-angiography has been recognized as the most reliable instrumental test for diagnosing brain death and is considered the gold standard.[19] When clinical criteria plus cerebral angiography, as used in our study, are combined, this approach is considered the gold standard for comparison.[18]

It has been emphasized that three specific clinical findings are necessary to confirm brain death: coma, absence of brainstem reflexes, and apnea.[18] Ancillary tests are needed when a neurologic examination cannot be performed. This has been confirmed in our patient group. Our results demonstrate that the absence of brainstem reflex responses resulted from the cessation of blood circulation in the brainstem and cerebral hemispheres.

Conclusion

Simple clinical bedside tests, including motor response to painful stimuli, the corneal reflex, and the pupillary response to light, were shown to be equally reliable as cerebral angiography in determining brain death. Therefore, confirmatory studies are not necessary to diagnose brain death. However, due to the regulatory requirements of the organ transplantation program, confirmatory testing is mandated in cases involving organ procurement.

Conflict of Interest

The authors declare no conflict of interest.

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