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Pitfalls and slip-ups in brain death determination

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Brain death (or brainstem death in the UK) is an uncommon result of a major catastrophic neurologic injury. The determination of brain death proceeds through a comprehensive and stepwise evaluation. There is no room for misinterpretations. Slip ups, however, could occur with brain death determination and this review discusses the most common concerns encountered by physicians. Problems may arise when a multitude of small errors accumulate and this may occur with an inexperienced physician who misjudges confounders, performs an incomplete evaluation, and misinterprets a confirmatory test.

Keywords: Brain death, Ancillary tests, Criteria, Pitfalls

Introduction

Brain death is an uncommon outcome of acute brain injury owing to the evolutionary resilience of the lower part of the brainstem with these types of injuries.[1,19] For brain death to occur in a patient, it requires further progression from an already catastrophic neurological injury and this is mostly seen with severe traumatic brain injury, aneurysmal subarachnoid hemorrhage, or fulminant meningoencephalitis. It is uncommonly a result of anoxic-ischemic injury or brainstem stroke. Only when asphyxia is profound and prolonged, such as in neonates and children, brainstem function can become permanently lost. The centrality of the brainstem in neurological criteria of death has been recognized by UK Royal College of Physicians and resulted in changing the term brain death into brainstem death. Neurologically, the condition is similar.

Overall, the number of brain deaths declared in patients has remained relatively stable in major US medical centers, although in some countries, there might be a decline due to improved care of patients with catastrophic injury and thus less likelihood of further deterioration.[2] Recognition of brain death may also have declined.[3]

Brain death determination requires a special skill set that in principle any physician can acquire, but we can make the argument that these complex evaluations are best reserved for neuro-intensivists or neurosurgeons frequently working in Neurosciences Intensive Care Units. Moreover, in the USA, a physician has an obligation to contact an organ donation organization if a patient is to suffer imminent brain death. The determination of brain death proceeds through a comprehensive evaluation that includes at least 25 different assessments and verifications. The American Academy of Neurology has provided a checklist that may assist physicians, but it is not clear if checklists reduce errors.[4]

There is no room for gross errors and no room for misinterpretations. In this review, I will discuss — and dispel — the 10 most common concerns in brain death determination and organ donation. More details can be found in another work.[5]

Concern #1: Experience of the Physician

Several brain death guidelines throughout the world have specifically mentioned the specialty of the physician. Many have required a neurologist or a neurosurgeon. There is no certification process, and that may be hard to justify and administer. The American Academy of Neurology stated that 'it seems reasonable to require that all physicians making a determination of brain death be intimately familiar with brain death criteria and have demonstrated competence in this complex examination'.[4] The recent pediatric guideline recommends that physicians should have specific training in neurocritical care to be competent to perform examinations in infants and neonates. The examinations should be performed by pediatric intensivists and neonatologists, pediatric neurologists and neurosurgeons, pediatric trauma surgeons, and pediatric anesthesiologists with critical care training. In addition, the guideline recommends that adult specialists should have appropriate neurological and critical care

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training to diagnose brain death when caring for a pediatric patient from birth to 18 years of age.[6]

Because brain death determinations are infrequent, general neurologists taking on hospital services occasionally who are called upon to declare a patient brain dead will rarely be able to acquire enough experience. Hospitals are therefore better off in identifying neurologists — or in larger institutions neurointensivists or hospitalists — who perform brain death determinations all the time. Inexperience of the physician, and not necessarily the specialty, may lead to inappropriate assessment of brainstem reflexes inadequate performance of the apnea test, or worse incomplete assessments. Many hospital practices stipulate two physicians, but it is unclear if this indicates a physician as an observer or if this is a second full examination. Any physician should have the opportunity to ask a colleague to confirm his clinical impression (I often have neurocritical care fellows, neurosurgery residents and nursing staff present). However, in adults, a time interval between two physicians is not necessary and could potentially lead to a major delay in brain death determination and in the worst case scenario the potential for loss of organs for donation due to premature cardiac arrest. In a recent study, it appeared that when such a waiting interval is stipulated, the true time between two examinations may increase three-fold.[7]

Inexperience of the physician may be evident in the inability to adequately test brainstem reflexes or apnea test for that matter, but may become magnified in the inability to identify potential confounders and the inability to accurately judge the validity of ancillary tests. Hospitals with training programs should not allow residents or fellows to declare patients brain dead without direct supervision.

Concern #2: Confounders

The evaluation of confounders and confounding drugs is fundamentally important and no examination should proceed if there is any lingering effect of drugs. A new concern is the evaluation of a patient who has recently been treated with therapeutic hypothermia, either to control fever initially, or in the setting of cardiopulmonary resuscitation. Often the clearance of drugs is underestimated and this specifically applies to the use of benzodiazepines and opioid infusions. It is possible that to control shivering significant amounts of these drugs may have been administered. Hypothermia will decrease liver metabolism that improves after rewarming, but there may be a delay to return to full function. In addition, reperfusion of previously cooled tissues may redistribute drugs and increase plasma levels of sedatives and analgesics administered during the cooling period. Brain death determination after therapeutic hypothermia for more than 24 hours is problematic and several days may be necessary to exclude the effects of previously administered drugs. The use of naloxone or flumazenil should be discouraged because of its brief effect and poor predictive value. There is no good advice to handle this situation, not knowing the clearance of these drugs and cardiologists should expect a reluctance of neurologists to proceed with brain death determination.

Other major confounders are misjudgment of alcohol effect, or failure to measure alcohol level before brain death determination. The presence of severe hypotension, severe acidosis, particularly in a patient with septic shock, and marked hypothermia (core temperature $<32^{\circ}C$) will markedly influence the examination of brainstem reflexes, may cause pupils fixed to light and mute oculocephalic responses. These reflexes may return after resuscitation. The attending cardiologist should understand that there is a reluctance to proceed with a brain death examination.

Concern #3: Inadequate Preparation for the Apnea Test

The apnea test requires preparation. This includes preoxygenation with a FiO_2 of 100% for 10 minutes. This procedure clears nitrogen in the alveoli that will improve oxygen diffusion. The apnea test fails if the patient has a significant A–a gradient due to inability of oxygen to pass the alveolar blood barrier. Presence of chest tubes (i.e. traumatic pneumothorax) also increases the probability of a failed apnea test. An abnormal chest X-ray, however, does not necessarily predict oxygenation difficulties during the test.[8] Oxygen desaturation after reduction of the positive end-expiratory pressure level to 5 cm of H_{20} indicates that disconnecting from the ventilator for the apnea test will lead to more oxygen desaturation.

The apnea test is best performed using an oxygen-diffusion method. Others have suggested using continuous positive airway pressure while keeping patients connected to the ventilator; however, in most ventilators, it is difficult to disable the alarm system. If the patient breathes — and often when set at maximal trigger sensitivities — it requires expertise to differentiate between a patient or a (false) ventilator induced waveform.

Other common errors are performing the apnea test in a markedly hypotensive patient, failure to provide adequate oxygenation during the apnea test, such as through a T-piece or worse no additional oxygen administration at all. Starting the apnea test with a low arterial pCO_2 (in the 20s) will take more time to reach the target (in the 60s) and could lead to unnecessary multiple arterial blood gas determinations.

Concern #4: The False Positive Signs of Brain Death Determination

There may be tests or signs that suggest brain death, but the patient is not. The most notorious false positive sign is a major intoxication. Detailed clinical neurological descriptions in intoxicated patients are mostly absent in the literature but CT scans of these patients are normal immediately pointing towards a major discrepancy.[9,10] Unsupported blood pressures with no need for vasopressors should also be a reason to give pause. Classically, the pupil response to light remains an important distinguishing feature and the light reflex remains in many cases of poisoning. A magnifying glass may be needed to appreciate pupillary contraction to light. Extreme forms of barbiturate intoxication, however, may result in loss of pupil reaction to light. Mydriasis (8 or 9 mm) or mid-position pupils (6 or 7 mm) can be seen after toxic exposure to antihistamines, tricyclic antidepressants, amphetamines, cocaine, phenylephrine, and other sympathicomimetics. Miosis (1–2 mm) points to any of the anticholinesterase agents, organophosphates, opioids, pilocarpine, and barbiturates or baclofen. Barbiturates and tricyclic antidepressants are best known, but in many instances, many brainstem reflexes remain intact and that will make the distinction easy. Brainstem reflexes can return after the patient is adequately resuscitated.

Most concerning is a recent report that despite several warnings, an organ donation protocol had been initiated in patient with baclofen intoxication.[10]

Concern #5: False Negative Signs of Brain Death Determination

The patient is brain dead but tests or signs suggest otherwise. The most common false negative signs of brain death are the presence of EEG activity or retained cerebral blood flow on a blood flow study or nuclear scan. Brain death has always been determined by clinical findings and these ancillary tests — despite showing blood flow or cortical neuronal activity — do not confirm or discount a functionally dead brainstem.

Occasionally — and much less common than reported — limb movements are seen also known as 'spinal reflexes'.[11–13] These movements most likely originate from the upper spinal cord and are often seen in neonates and children. Forceful neck flexion may result in slow or abrupt rising of the arm or finger flexion. Most of these spinal reflexes are seen after being provoked by a noxious stimulus or even touch and do not occur spontaneously. In some patients, spontaneous — again very slow — head turning to one side may occur. Most frequently, a vigorous triple flexion response with noxious stimuli to the toe can be found during examination and the responses may remain for hours.[12]

Another sign that is often misjudged is ventilator auto-triggering. The ventilator is at fault and recognizes minor pressure or volume changes in the tubing and that is 'read' by the ventilator as a patient effort and results in triggering. Water in the circuit is a common reason, but the ventilator may also have been set on a high trigger sensitivity. Changing these thresholds will correct the problem and a repeat apnea test is seldom needed.

Concern #6: Is Brain Death Different in Children?

Due to maturational lag, brain death determination in newborns may be more complicated and the examination is certainly unreliable in preterm infants. There have been sporadic reports of 'recovery' of infants, but each case has extraordinary flaws[14] (i.e. confounders, incomplete examination, or uncertain irreversibility of the brain injury). The new pediatric guideline indirectly leaves open the possibility of change in examination and stipulates that a newborn, defined as >37 weeks of gestational age to 30 days, will need two examinations by two separate physicians and 24 hours apart. A child from 30 days to 18 years requires two examinations by two separate physicians and 12 hours apart.[6] The age brackets and repeat examinations in the new pediatric guidelines — evidently used as an additional safeguard — are not based on prospective data. Physiologically, children are not much different than adults, and after several months, they are neurologically no different from adults either.[15]

Pediatricians have been struggling with brain death determination and part of the problem is lack of recent large detailed series of patients that could provide guidance. In the end, the clinical determination of brain death in adults should not be different from young adults and children.

Concern #7: Overreliance on Ancillary Tests

Errors in brain death determination may have to do with misinterpretation of ancillary tests. Cerebral blood flow studies would seem so simple and straightforward: no flow — dead brain. However, the nuclear scan — uptake is a reflection of cerebral blood flow — is difficult to interpret with certainty and experience of radiologists with interpretation of this test varies. Ideally, flow should stop at the dura, and this is the case in patients who have had their tests performed after several days of extraordinarily high intracranial pressure that leads to very low cerebral perfusion pressures and vascular collapse. The results of cerebral blood flow studies are primarily dependent on the cerebral perfusion pressure, thus low cerebral perfusion pressure results in no flow — not very low cerebral perfusion pressure results in still some flow and either of which can be observed in clinically dead patients.

Discrepancies between flow studies and between flow studies and electroencephalographic studies (EEG) are not uncommon. Physicians cannot choose between two tests and some may order a third test that most likely also is ambiguous. The EEG is very susceptible to significant artifacts in the intensive care unit. Evoked potentials are already abnormal in severe cortical or brainstem injury with many retained brainstem reflexes and basically invalidate its usefulness in brain death.[16] Any pump, ventilator, or even more complex set-ups such as extracorporeal membrane oxygenation could make the interpretation of EEG virtually impossible. No physician wants to declare a patient brain dead — using an ancillary test to override a confounder — and be told by the nursing staff that there has been return of eye movements, purposeful motor movement, or spontaneous breathing.

Concern #8: Appropriately Supporting Families and Discussion of Organ Donation

In the USA, requests for organ donation must go through an organ donation agency, but in other countries, physicians have the responsibility to discuss organ donation. When organ donation is discussed too soon, refusal for organ donation is more likely. When organ donation is discussed without an experienced organ transplant coordinator, the chance of refusal doubles. Therefore, nursing staff and the treating medical team should hold off on any discussion before and after brain death determination.

The physician should have a good rapport with family members and explain exactly what determinations are done and at what time point. A request for organ donation requires a considerable amount of explanation, time, and effort and this responsibility should not be underestimated. Families should be adequately prepared and supported in their bereavement.

Concern #9: Failure to Maintain a Suitable Organ Donor

In the USA, the maintenance of donor management is in the hands of an organ procurement agency, but many problems can arise before the care is fully handed off. A brain death donor is physiologically unstable. Patients become rapidly hypothermic, hypotensive, develop diabetes insipidus, may develop cardiac arrhythmias and, over time, develop pulmonary edema.[17,18] It is important to set goals for management of the potential organ donor and these are: maintenance of systolic blood pressure of >100 mmHg or a mean arterial pressure of more than 70 mmHg; adequate urine output defined as at least 0.5 ml/kg/h; normal serum electrolytes, including normal sodium, potassium, calcium, magnesium, phosphate and glucose.

Lung protective ventilation is essential with a tidal volume not more than 8 ml/kg, with minimal positive end-expiratory pressure if possible. Excessive IV fluids should be avoided. Vasopressor drugs are required and usually include vasopressin to reduce catecholamine requirement.

Concern #10: Failure to Look for Alternative Options for Organ Donation

If the patient does not progress to brain death and care is futile, the patient — when age is less than 60 years — could potentially become a candidate for donation after withdrawal of life support. Organ and tissue retrieval is in the operating room after the patient becomes apneic and circulation stops. Retrieval proceeds after an additional 5 minutes after circulatory arrest has been observed. This procedure is known as donation after cardiac death (DCD) protocol and is only set in motion after end-of-life decisions have been made. To maintain accreditation, hospitals in the USA are now required to have a DCD protocol in place. A DCD procurement protocol is more complicated and regulated than a brain death procurement protocol. Eligibility of patients for a DCD protocol is best determined by a different physician and a coordinator in order to avoid the potential for involvement with end–of-life decisions. Nonetheless, an organ procurement coordinator needs to be notified in any patient with withdrawal of support. Every year, patients are lost to donation due to lack of referral.

Conclusions

There are many subtleties and concerns with brain death determination. Brain death determination requires professionalism and a skill set that can only be acquired after many years of brain death determinations. Hospitals could benefit from specifically recognizing physicians who will perform these examinations. Errors in brain death may lead to a 'perfect storm'. This situation is best described as an inexperienced physician who misjudges confounders, performs an incomplete evaluation, misinterprets a confirmatory test, and may even tell family members their loved one is brain dead. But in all honesty there is no need for alarm and virtually all circumstances of brain death determination is without slip-up or errors. Brain death determination is also — fortunately so — linked to organ donation in nearly 70% of the cases.

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