Ancillary Studies in Evaluating Pediatric Brain Death

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Abstract

When confounding variables exist that inhibit the ability to diagnose brain death clinically in pediatric patients, ancillary tests may provide additional information for the practitioner in evaluating for the presence or absence of brain death. Multiple options exist but differ in availability, ease of administration, cost, safety profile, and reliability to accurately diagnose brain death. An important desirable quality of an ancillary test is eliminating false positives, which imply brain death when brain death is in fact not present. More commonly available ancillary studies include electroencephalograms, brain angiography through various modalities, brain stem auditory evoked potentials, and transcranial Doppler ultrasound. At this time, there is not an ancillary test with 100% reliability in diagnosing brain death that can replace the clinical brain death exam. Therefore, practitioners need to understand the strengths and limitations of the ancillary studies available at their hospital.

Keywords

- ▶ pediatric
- ▶ brain death
- ▶ ancillary

Introduction

The diagnosis of brain death carries great importance for several reasons including closure for the patient and family as well as the possibility for organ procurement. The clinical diagnosis of brain death may be made following two clinical exams consistent with brain death, including apnea tests, separated by a defined period of time. In these situations, ancillary studies are not required to make the diagnosis of brain death.¹ However, there are times when confounding patient factors may inhibit the ability to make a clinical diagnosis. Examples of such confounding factors are listed in ▶Table 1. In this situation, a variety of ancillary tests may aid in the diagnosis of brain death (▶Table 2). Ancillary testing may be used in conjunction with the clinical exam to support the diagnosis of brain death. Ancillary studies should not be used to replace the brain death neurological exam and apnea test. The clinical exam should still be completed to its fullest

extent twice on each individual and documented even when an ancillary test suggests brain death.

Countries throughout the world have differing guidelines concerning the use of ancillary brain death testing. An international survey in 2002 found 33% of countries worldwide and 38% of European countries required mandatory confirmatory ancillary brain death testing.² However, this is not universally agreed upon and the 2011 multidisciplinary committee guidelines for determination of brain death in infants and children specifically state ancillary tests are not required to make the diagnosis of brain death.¹ The most useful ancillary test has 100% reliability, therefore not having any false positives, implying brain death when brain death is not present, and thus a high specificity. False negatives, denoting no brain death when brain death is in fact present, although not desirable, are more acceptable than false positives. The ideal ancillary test will also provide 100% reliability in diagnosing brain death on its own merit and will be

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Table 1 Brain death confounding variables

Hypothermia
Hypotension
Presence of central nervous system sedatives
Presence of sedating antiepileptics
Severe facial trauma
Inability to perform apnea test:
Neuromuscular disease or paralysis
High C-spine injury
Pharmacological paralysis
Severe lung disease

readily available at the bedside, present in all hospitals, inexpensive, easily administered, safe, provide easily interpretable results, and not be susceptible to confounders such as hypotension or sedative medications.³ Unfortunately, the perfect test does not exist at this time. Current ancillary tests, their qualities and deficiencies will now be discussed.

Electroencephalography

An electroencephalogram (EEG) is a noninvasive test that can be easily performed at the bedside. When performing an EEG to evaluate for brain death, one must avoid hypotension and hypothermia. An EEG is perhaps the oldest ancillary test to aid in the diagnosis of brain death. In 1968, a Harvard committee examining the definition of brain death included a flat EEG as one of the tests required to define brain death.⁴ The recommendation was that an EEG should be utilized if available. Furthermore, in 1977, the American Neurological Association stated the EEG to be "a valuable confirmatory indicator of brain death and its use is strongly recommended."⁵ In the largest pediatric study to date, Ruiz-García et al reported the use of EEG in evaluating 122 brain-dead pediatric patients younger than 18 years of age. Of the 122

patients, 111 (91%) were found to have an isoelectric EEG.⁶ It has been suggested that a false-negative result (brain electrical activity when the patient is brain dead) may occur secondary to background artifact.⁶ In a summary of EEG data from 12 different studies encompassing 485 suspected brain-dead pediatric patients, EEG results were consistent with brain death in 89% of patients.¹ Only twice did a patient have an active EEG on a follow-up EEG after previously described electrocerebral silence. In both cases, the patients were being treated with barbituates.^{1,7,8}

EEGs have been critiqued for multiple reasons. First, EEG recordings are produced by the cortical superficial brain and not the deep layers of the brain including the brain stem. The captured EEG frequencies recorded do not include frequencies < 0.5 or > 35 Hz.³ Therefore, deeply located, live neurons may still be present despite an isoelectric EEG.³ In addition, EEGs can be altered on patients who are hypotensive, hypothermic, or receiving sedatives. As discussed earlier, EEGs can produce both false-negative and false-positive results.

Cerebral Angiography

Cerebral angiography has long been the gold standard for diagnosing brain death.¹ However, image variability can occur secondary to the position in which the aortic arch is injected and depending on the technique used in pushing the injectate.⁵ Cerebral angiography is invasive, not readily available and requires a physician skilled and credentialed to perform it. The absence of blood flow through the four arteries supplying blood to the brain, internal carotid, and vertebral arteries, along with good perfusion to the extracranial vessels, confirms brain death.^{9,10} At one time, this was the most reliable and practical confirmatory test to perform. However, technological advances have allowed the development of relatively noninvasive means to evaluate brain perfusion.

Radionuclide Angiography

Radionuclide angiography (RA) is often used as a confirmatory ancillary test for brain death due to availability and affordability.¹¹ Many centers are able to perform bedside testing and RA has been extensively studied, in adults especially, for more than 30 years.^{12,13} In 1986, Coker and Dillehay reported brain death confirmation in 55 pediatric patients via radionuclide cerebral imaging.¹⁴ Of interest, 14 of 55 children had persistent dural sinus activity but no cortical flow. Likewise, Shimizu et al had 27 brain-dead pediatric patients undergo RA with all tests confirming brain death by showing no cerebral flow.¹⁵ In a review by Heran et al, RA was validated for brain death testing, but only when used with spectroscopy.¹⁶ One pediatric case report of a patient with trisomy 18 and EEG silence demonstrated normal cerebral blood flow on RA, suggesting RA to be more accurate than EEG in brain death evaluation.¹⁷ Despite its described usefulness, RA is limited in that it does not fully demonstrate the posterior fossa and its blood flow;

Table 2 Ancillary tests for brain death

Electroencephalogram
Cerebral angiography
Radionuclide angiography
Computed tomography angiography
Magnetic resonance imaging/angiography/venography
Magnetic resonance perfusion/spectroscopy
Brain stem auditory evoked potentials
Xenon computed tomography
Single-photon emission computed tomography
Transcranial doppler ultrasound
Atropine test

therefore, a patient could potentially have brain stem flow and RA showing no flow. Therefore, despite one review arguing that “arbitrary waiting period, withdrawal of sedative drugs, or electrophysiological studies are not needed,” RA should always be accompanied by a clinical exam, even if limited, confirming brain death.^{11,13}

Computed Tomography Angiography

Computed tomography angiography (CTA) is usually readily available at all times of the day or week and can be performed quickly at most hospitals. However, at this time, there is not a consensus on what specific radiographic criteria need to be present or absent to confirm brain death by CTA. A 2010 American Academy of Neurology subcommittee stated that there was insufficient evidence to justify the use of CTA in neurological brain death.¹⁸ Interpretation of CTA may also prove to be difficult depending on the expertise of the physician evaluating the study. Other pitfalls concerning CTA include the possibility to miss slow flow states because of rapid acquisition of images and the occurrence of retained blood flow.⁵ In a meta-analysis of 12 studies with 541 patients describing CTA criterion for brain death, diagnostic accuracy was highly dependent on the criteria used to classify cessation of intracranial blood flow. Various criteria used for brain death diagnosis include the combined absence of opacification of the distal branches of the middle cerebral artery and the internal cerebral veins (French guidelines), no intracranial arterial phase opacification, no intracranial arterial or venous phase opacification, lack of internal cerebral vein opacification, and different combinations of the aforementioned criteria.¹⁸ Sensitivity of the pooled data varied between 62 and 99%. However, specificity, relating to declaring brain death when brain death is not present, could not be determined from the data. Another downside of CTA is the use of potential nephrotoxic intravenous contrast, which could adversely affect renal function. At this time, CTA needs to be better studied in relation to its use as an ancillary study for brain death.

Magnetic Resonance Imaging/Angiography/Venography

Magnetic resonance imaging/angiography (MRI/MRA) and magnetic resonance venography (MRV) have been evaluated for potential use in diagnosing brain death. MRI is noninvasive and accurate, but not routinely available 24 hours a day, not a bedside test, and difficult to obtain in a critical patient requiring magnet sensitive ventilation equipment, infusion pumps, and temperature probes. Tonsillar herniation and downward displacement of the brain stem can be evident on MRI evaluation and is a suggested method to diagnose brain death.¹⁹ MRA may identify lack of intracranial arterial flow, which also may suggest brain death. However, there is concern about the sensitivity of MRA to slow blood flow that may mimic lack of blood flow. MRV can be used to visualize the intracranial veins with the lack of visualization of intracranial veins inferring lack of intracranial circulation

and brain death. However, partial filling of intracranial veins may still be seen despite evidence of tonsillar herniation and no MRA arterial flow.¹⁹ Decreased quality of images secondary to the limited magnet strength and magnetic field can produce problems evaluating respective studies.¹⁹ Further studies on MRI/MRA sensitivity and specificity need to be performed in relation to diagnosing brain death.

Magnetic Resonance Perfusion and Magnetic Resonance Spectroscopy

Magnetic resonance (MR) perfusion and MR spectroscopy studies have also been used to evaluate brain death in patients. Diffusion-weighted imaging (DWI) was thought to be potentially useful after two studies demonstrated decreases in apparent diffusion coefficient in the parenchyma of clinically diagnosed brain-dead patients.^{20,21} However, DWI lacks the specificity and sensitivity to predict global brain function.¹⁶ MR spectroscopy would likely demonstrate metabolite derangements, in lactate, for example, with neuronal death, but these are late findings not often seen on initial study.²² Another study looked at nonproton MR spectroscopy using sodium- and phosphorus-based techniques trying to specifically look at adenosine triphosphate-dependent pathways or neuronal membrane integrity,²³ but these tests have not been validated.¹⁶ Therefore, the sensitivity and specificity of MR perfusion and MR spectroscopy are lacking and cannot be recommended as a formal ancillary test useful in evaluation of the potential brain-dead patient at this time.

Brain Stem Auditory Evoked Potentials

Brain stem auditory evoked potentials (BAEPs) have also been evaluated as a brain death ancillary test. BAEPs have been of particular interest because of the noninvasive nature of the test and reported ability to perform the test despite the presence of hypothermia or barbituates.²⁴ BAEPs use recordings from scalp electrodes to detect far field potentials deep in the brain. They can allow investigation of specific areas of interest related to the brain stem, but are an incomplete assessment of global brain function secondary to measuring only individual discrete pathways in the brain. Abnormalities in such pathways may eliminate the evoked potential while still sparing the other brain stem structures.³ Therefore, BAEPs are limited to the restricted pathways and do not test for functional integrity of the central nervous system structures.³ Ruiz-López et al reported results of BAEPs in 51 brain-dead pediatric patients. BAEPs following the establishment of brain death were compatible with brain death in 45 of 51 patients.²⁵ However, only 27 of these patients had a complete lack of BAEP, while the others had varying responses. This prompts discussion of what constitutes brain death in relation to BAEP. In another study, Ruiz-García et al studied BAEPs and somatosensory evoked potentials (SSEPs) in 107 clinically brain-dead pediatric patients and found 100 of 107 patients with no BAEP or SSEP confirming brain death. When correlated with clinical exam, BAEPs can provide

additional information about potential brain death.^{24,26} However, secondary to evoked potentials not measuring brain stem functionality, results of BAEPs should be carefully interpreted in patients being assessed for brain death.

Xenon Computed Tomography

Xenon CT involves inhalation of the gas xenon with subsequent quantitative cerebral imaging. This avoids the use of contrast that is often required by many other ancillary tests and can potentially preserve kidney function if organ donation is pursued following brain death. Xenon CT is noninvasive, rapid, and provides quantitative measurements of cerebral blood flow.²⁷ In a 30-patient study where all patients met clinical criteria for brain death, xenon CT was performed after 4.5 to 6 minutes of xenon inhalation.^{3,28} Average global cerebral blood flows of $< 5 \text{ mL}/100 \text{ g}\cdot\text{min}^{-1}$ is claimed to be confirmatory of brain death. Of 30 patients, 10 meeting clinical brain death criteria had areas of the brain with higher xenon flow than $5 \text{ mL}/100 \text{ g}\cdot\text{min}^{-1}$ and 3 of these patients showed normal xenon cerebral blood flow. In addition, two of the three patients with normal xenon flow had EEG electrocerebral silence. Accessibility of xenon CT remains challenging with only a select number of North American academic institutions having access to the technology.¹⁶ At this time, further evaluation of xenon CT needs to be performed prior to consideration of use in ancillary brain death testing.

Single-Photon Emission Computed Tomography

Single-photon emission CT (SPECT), also referred to as Tc-99m hexamethylpropyleneamine oxime SPECT, has been described as a functional and available modality to confirm brain death.²⁹ SPECT has limited availability at most institutions but has been stated to be a reliable indicator of brain death in adults.²⁹ Lack of radionuclide signal within the brain demonstrates an “empty skull” appearance consistent with no intracranial blood flow. Okuyaz et al performed a study in eight pediatric patients found to be clinically brain death as well as having EEG electrocerebral silence. Patient age ranged from 7 days to 8 years. Results of a single SPECT test demonstrated “empty skull” results in six patients, ages 2 to 8 years. However, two patients, both newborns 7 days of age, demonstrated flow in their first SPECT study. In repeat studies 5 days later, both newborns demonstrated no intracranial blood flow.²⁹ In addition, intracranial blood flow has been demonstrated in patients found to be clinically brain death and no flow found in patients who were not clinically brain death making the use of SPECT highly questionable for newborns.³⁰ Otherwise, outside the newborn period, brain death ancillary evaluation with SPECT may be a promising option, if available.¹⁶

Transcranial Doppler Ultrasound

Transcranial Doppler ultrasound is a noninvasive bedside test, relatively inexpensive, can be quickly performed, and

overall widely available. Patients must have a normal blood pressure during testing. Transcranial Doppler ultrasound has several limitations. A skilled ultrasonographer must be available to complete the exam and an experienced practitioner must be able to interpret the results. It has been suggested, for consistency, that the same ultrasonographer performs multiple exams.³¹ Obtaining an ultrasound image of the basilar artery includes turning the patient on their side and flexing the neck with the chin touching the chest. The ability to do this in a critically ill patient, especially in a patient with suspected cervical spine injury, may be restricted.

Transcranial Doppler ultrasound evaluates intracranial arterial blood flow in relation to intracranial pressure (ICP). Multiple stages have been described with respect to the waveform obtained by a pulsed Doppler ultrasound in the cerebral arteries. As ICP increases, there is first a reduction in the diastolic flow velocities of the Doppler waveform which will then disappear as ICP reaches diastolic blood pressure. With further increases in ICP, retrograde diastolic blood flow, also referred to as reverberating or oscillating flow, occurs secondary to the ICP being greater than the diastolic blood pressure. Further increases in ICP may lead to “systolic spikes” which are seen when the ICP reaches the systolic blood pressure.^{31,32} Finally, it is possible to have complete absence of flow and waveform when the ICP value exceeds systolic blood pressure. The presence of either retrograde diastolic blood flow, systolic spikes, or absence of flow documented by transcranial Doppler ultrasound is said to be diagnostic of cerebral circulatory arrest.^{31,33} For documentation of brain death, it has been recommended that the presence of cerebral circulatory arrest be confirmed in two separate studies at least 30 minutes apart.³¹ Lack of flow in the middle cerebral arteries may precede the loss of spontaneous respirations.³¹ Therefore, cerebral circulatory arrest consistent with brain death in both middle cerebral arteries as well as the basilar artery should be confirmed.³¹

The sensitivity of transcranial Doppler ultrasound in diagnosing brain death has been reported as 89% with a specificity of 99%.³⁴ Therefore, there are several false negatives. This could potentially delay the diagnosis of brain death. One such patient satisfied clinical brain death but persistent flow on transcranial ultrasound delayed the diagnosis of brain death and subsequent organ donation.³² Cerebral blood flow may still be detected in clinically brain-dead patients with open skulls or with anoxia as the cause of death.³⁵ There have also been several false positives in the literature where reversal of diastolic flow was observed during increased ICP.³⁶ This gives further credence to performing multiple exams 30 minutes apart.

Atropine Test

An “atropine test” is based on the premise that there is a void of parasympathetic influence from the vagal dorsal nucleus on heart activity in brain-dead patients. It is an inexpensive test that can be easily administered at the bedside; 2 mg of atropine is administered intravenously and a negative test

result is defined as a change in heart rate less than 3%. A negative test would confirm the destruction of the intracranial parasympathetic system. Several things need to be considered when considering an atropine test as a confirmatory test. It is possible to have a negative atropine test in brain-dead patients with skull defects including decompressive craniectomies, open fontanelles, and traumatic injuries subsequent to brain stem damage despite continued cerebral perfusion. Damage to the vagal dorsal nucleus without brain stem death could also result in a negative atropine test. In addition, autonomic neuropathies may not respond to atropine and heart transplant recipients will already have cardiac denervation. Finally, one must consider giving atropine to neurologically injured patients where the pupillary exam may be affected for an extended period of time.³⁷

Conclusion

Individual clinicians should always use traditional brain death and apnea testing if at all possible. At this time, ancillary testing is not able to replace the clinical bedside exam as there is no perfect ancillary test for brain death testing. Even more, pediatric literature is lacking in quantitative or qualitative data to support one test over another. Each ancillary test presents its own set of challenges including, but not limited to, facility resources, provider skill at interpreting the results, technician ability to perform the test, and specificity of each test in its ability to detect brain death. Physicians evaluating a potentially brain-dead patient must understand the ancillary tests available at their individual centers and appreciate the strengths and limitations of each test.

Conflict of Interest

None.

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