CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Determination of Brain Death

David M. Greer, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

From the Boston University School of Medicine and Boston Medical Center — both in Boston. Dr. Greer can be contacted at dgreer@bu.edu or the Department of Neurology, 85 East Concord St., Rm. 1145, Boston, MA 02118.

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A 52-year-old man undergoes cardiac arrest while at work. He is revived after 40 minutes of cardiopulmonary resuscitation, and on arrival at the hospital he undergoes targeted management of his body temperature, which is maintained at 36°C for 24 hours. He is rewarmed to a temperature of 37°C over the ensuing 4 hours. The next day, he is comatose, with no brainstem reflexes and no movement in his arms or legs other than bilateral triple-flexion signs in response to noxious stimulation. He is no longer breathing at a higher rate than that set on the ventilator. Vasopressor medications are required to maintain a systolic blood pressure above 100 mm Hg, and global anoxic injury is observed on computed tomography (CT) of the brain (Fig. 1). How would you establish the diagnosis of brain death?

THE CLINICAL PROBLEM

An audio version of this article is available at NEJM.org

Brain death, or death as determined according to neurologic criteria, accounts for approximately 2% of adult[1] and 5% of pediatric in-hospital deaths in the United States.[2] Brain death is a direct by-product of the invention of mechanical ventilation; previously, a patient with a neurologic catastrophe would simply become apneic; hypoxia would ensue, and the heart would stop beating shortly thereafter. In the 1950s, a new neurologic state was described in which ventilated patients with cerebral catastrophes showed complete unresponsiveness (coma) and had loss of all brainstem reflexes, apnea, and isoelectric readings on electroencephalography (EEG) (a condition termed "le coma dépassé").[3] Subsequent work led to the Uniform Determination of Death Act, which provides a legal basis for brain death, described as "irreversible cessation of all functions of the entire brain, including the brainstem."[4]

Today, brain death is widely accepted conceptually and legally worldwide.[5] Although protocols may vary, both within[6] and among countries,[7] the basic concepts remain the same: the determination is made clinically, although ancillary testing is sometimes necessary or even mandated. Etiologically, brain death can occur by means of a cerebral insult that is primary (subarachnoid hemorrhage, traumatic brain injury, intracerebral hemorrhage, massive ischemic stroke, or, in rare instances, cerebral neoplasm) or secondary (most commonly cardiac arrest with global anoxic brain injury). Regardless of the cause, the final common pathway involves massive increases in intracranial pressure leading to compromise in cerebral circulation, with secondary anoxic brain injury; the process is completed when the intracranial pressure exceeds the mean arterial pressure, and cerebral circulatory arrest ensues.[5] The loss of brain function typically progresses from rostral to caudal, with loss of brainstem function occurring last, owing to the

KEY CLINICAL POINTS

DETERMINATION OF BRAIN DEATH

- Brain death, or death as determined by neurologic criteria, accounts for approximately 2% of adult and 5% of pediatric in-hospital deaths in the United States each year.
- Determination of brain death is typically made clinically and requires demonstration of the permanent loss of function throughout the brain, including the brainstem, in the absence of factors that may confound the assessment, such as temperature or blood-pressure dysregulation, electrolyte or acid–base disturbances, or toxins or medications.
- If confounding factors cannot be eliminated, or if the examination cannot be safely or fully performed, ancillary testing is performed (typically in the form of cerebral blood-flow studies that evaluate for the complete loss of cerebral circulation).
- The use of therapeutic hypothermia or extracorporeal membrane oxygenation complicates but does not preclude the determination of brain death.
- The determination requires meticulous attention to technique, with careful avoidance of potential pitfalls that may lead to misdiagnosis.

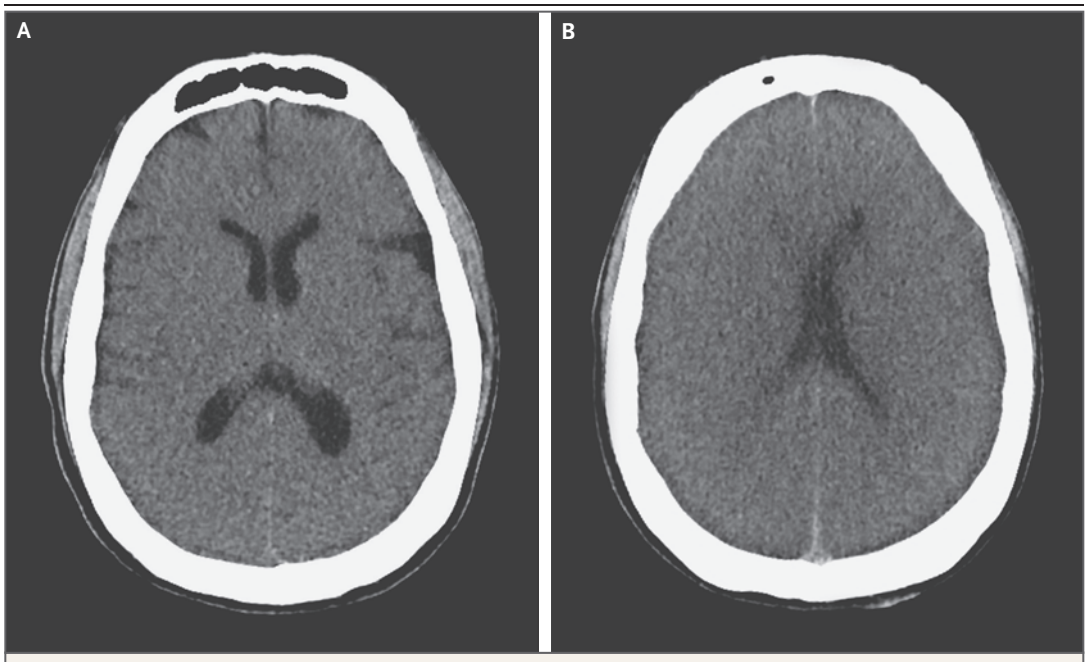

Figure 1. Findings on Computed Tomographic Imaging Consistent with Brain Death.

The loss of differentiation between gray matter and white matter, the obliteration of the basal cisterns, and the presence of global cerebral edema with diffuse effacement of the sulci and lateral ventricles are consistent with severe diffuse anoxic injury. Panel A shows the level of the basal ganglia, and Panel B a higher level in the lateral ventricles. The images were obtained from the same patient.

relative resilience of the brainstem to anoxic injury. Within the brainstem, the medulla is the last to cease functioning, as reflected in the loss of respiratory drive. Careful clinical assessment is necessary to ensure that the determination of brain death is accurate and to maintain trust and open communication with a patient's loved ones.

Before testing is considered, the clinician must know the underlying cause of the neurologic catastrophe and confirm that it is compatible with brain death and must ensure the absolute irreversibility of the condition. Establishing irreversibility usually entails a waiting period, the duration of which depends on the cause of the catastrophe. In cases of global anoxic brain injury after cardiac arrest, a minimum waiting period of at least 24 hours is standard, although its necessity has not been systematically studied.

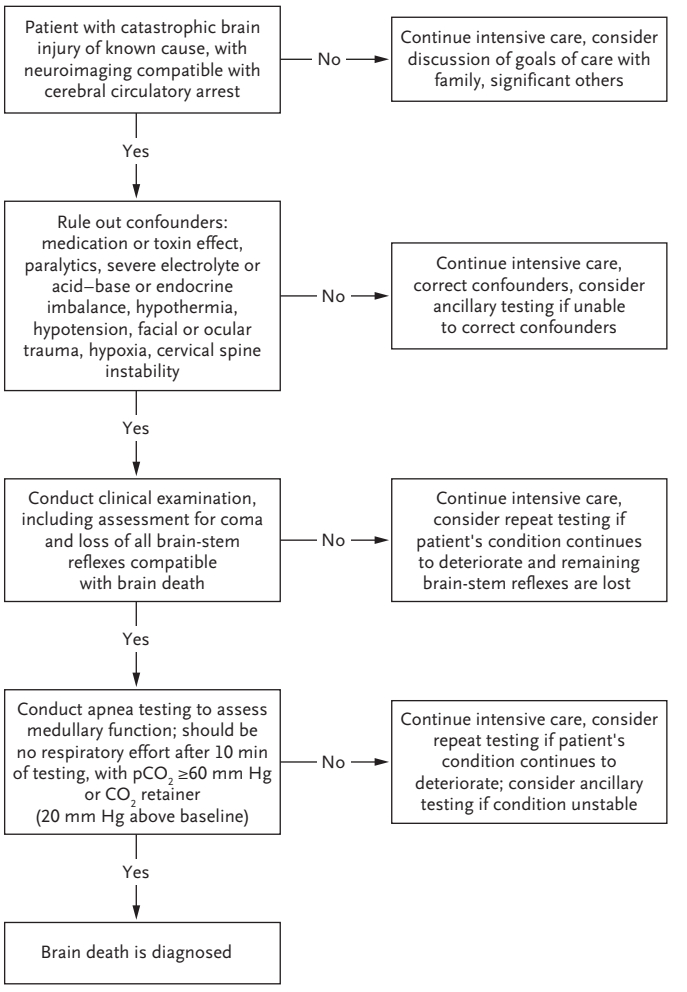

Figure 2. Algorithm for the Determination of Death According to Neurologic Criteria.

In children, a minimum of two separate clinical examinations is required to make a determination of brain death,[8,9] with the most recent U.S. guidelines recommending an intervening period between the two examinations of 24 hours for neonates (37 weeks of gestation up to 30 days of age) and 12 hours for infants and children (31 days of age up to 18 years of age)[9]. However, data are lacking to support these recommendations, and the waiting period between two examinations is most likely unnecessary as long as an adequate waiting period precedes any clinical determination.

Adult guidelines require one or two examinations,[10,11] and evidence suggests that one may be sufficient. Among more than 1400 cases (largely in adults) in which brain death was determined with the use of two examinations,[12,13] there were no instances in which the second examination was inconsistent with the first. Nonetheless, many states and institutions require two examinations — a more conservative approach.

STRATEGIES AND EVIDENCE

DETERMINATION OF BRAIN DEATH

The process for determining brain death includes five components: ensuring that certain prerequisites are met, neurologic examination, apnea testing, ancillary testing (if necessary), and documentation (see Fig. 2).

PREREQUISITES TO DETERMINATION

Numerous criteria must be met before a determination of brain death. In addition to determining the underlying cause of death and ensuring irreversibility, clinicians must be aware of factors that may confound the determination. These include dysregulation of temperature, blood pressure, electrolyte levels, acid–base status, and intoxication, including from self-administered toxins (e.g., opioid overdose) or medications received during the course of treatment (e.g., benzodiazepines or barbiturates) to prevent seizures or to treat elevated intracranial pressure. It may sometimes be necessary to administer a fluid bolus or vasopressors to ensure adequate blood pressure. Drug metabolism may be slowed (and drug clearance prolonged) in many patients, especially after cardiac arrest, owing to concomitant hepatic or renal injury or to hypothermia that may result from environmental exposure or from therapeutic measures, not only those commonly taken after cardiac arrest but also second- or third-line measures used to control elevations in intracranial pressure.[12] Failure to account for persistent effects of central nervous system depressants is one of the most common causes of false determination of brain death. As a general rule, clinicians should allow as much time as deemed appropriate in a given clinical situation to ensure that testing is accurate (e.g., waiting for at least five half-lives of a potentially confounding medication) or, when confounding factors cannot be excluded, perform ancillary testing.

CLINICAL EXAMINATION

The clinical examination conducted for the determination of brain death requires meticulous technique and maximal stimulation (see Table 1 and video, available with the full text of this article at NEJM.org). Coma is established by the absence of responsiveness to all noxious stimulation, including auditory, visual, and tactile stimulation. Pressure should be applied not only to the trunk, arms, and legs but also to the supraorbital notch and the temporomandibular joint; the last two sites are especially important in persons with a high cervical cord injury or severe peripheral neuropathy that might preclude a response owing to absent sensory or motor pathways. Spinally mediated responses must be distinguished from those of cerebral origin (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Although much of the brainstem examination has remained consistent over decades, there have been advances in assessing pupillary reactivity. Automated pupillometers are a useful adjunct to light-emitting diode testing and may be more sensitive than a standard light, but they have not been validated for use in the determination of brain death; nonetheless, detection of pupillary reaction by either method precludes determination of brain death.[13] Many clinicians test the corneal reflex incorrectly or insensitively, failing to provide adequate stimulation regarding intensity or location; light, direct application of pressure adjacent to the iris is recommended.[14] Although it may not always be possible to perform the oculocephalic ("doll's eye") maneuver (e.g., in cases of injury to the cervical spine), it is almost always possible to perform the oculovestibular (or caloric) reflex test. If substantial portions of the clinical examination cannot be

A video showing examination to determine brain death is available at NEJM.org

Table 1. Clinical Examination to Determine Brain Death.

Test	Regions Tested	Indications of Brain Death	Cautions
Consciousness	Rostral brainstem, thalamus, bilateral cerebral hemispheres	No response to noxious auditory, visual, or tactile stimulation	Use of adequate stimulation is important, including noxious tactile stimulus of the cranium (supraorbital notch and temporomandibular joint, intranasal stimulation) as well as the torso and limbs
Pupillary reflex	Upper brainstem	No response to bright light	Use of medications may affect pupillary reactivity History of corneal trauma or ophthalmic surgery may affect reactivity Quantitative pupillometry may be a useful adjunct for detection of subtle reactivity
Corneal reflex	Middle-to-upper brainstem	No eyelid response when pressure is applied at the border of iris with a cotton swab on a stick	Use of adequate pressure should be ensured; the lateral conjunctiva, which is less sensitive than the proximal conjunctiva, should be avoided
Oculocephalic reflex ("doll's eye" maneuver)	Middle brainstem	No eye movement with head turning	Use of this approach should be avoided when the integrity of the cervical spine is questionable
Oculovestibular reflex ("cold caloric" reflex test)	Middle brainstem	No eye movement within 60 seconds of instillation of ice water	Clear pathway to intact tympanic membrane should be ensured; head should be elevated to an angle of 30 degrees; wait 5 minutes between testing of each ear
Gag reflex	Lower brainstem	No gag reflex in response to bilateral stimulation of the posterior pharynx with a tongue depressor or suction catheter	Avoid manipulation of endotracheal tube, if present
Cough reflex	Lower brainstem	No cough in response to deep bronchial suctioning	May be absent in patients with phrenic nerve palsy resulting from injury to the cervical cord
Motor response	Brainstem, cerebral hemispheres	No cerebrally mediated response to deep nail-bed pressure or proximal stimulation of trunk or arms and legs	May be difficult to distinguish spinally mediated responses from cerebrally mediated responses; expertise and, in some instances, ancillary testing may be required

performed (e.g., in cases of postsurgical pupils or facial trauma), ancillary testing may be required.

THE APNEA TEST

Apnea testing assesses function of the medulla by allowing carbon dioxide levels to rise and the pH to fall sufficiently to maximally stimulate medullary respiratory centers; the absence of respiratory effort in response to hypercarbia and acidosis is consistent with brain death. Decisions regarding apnea testing must take into consideration the patient's pulmonary and hemodynamic stability. The main risk is cardiovascular collapse, which can be mitigated by ensuring adequate oxygenation before testing. Apnea testing should only take place in an intensive care setting with continuous blood pressure and oxygenation monitoring and after all other clinical testing is consistent with brain death. After normocarbia and a normal pH have been established, and preoxygenation has been provided, typically to a partial pressure of oxygen above 200 mm Hg, the patient is temporarily disconnected from the ventilator, with oxygenation preserved through passive diffusion through a catheter placed in the lower trachea (flow rate of 4 to 6 liters per minute). For 10 or more minutes, the patient is observed for any signs of respiratory effort (the presence of which would exclude brain death); if no respiratory effort is made, arterial blood gas analysis must show a partial pressure of carbon dioxide of at least 60 mm Hg, or 20 mm Hg above a known elevated baseline (e.g., in persons known to retain carbon dioxide, such as in some patients with chronic obstructive pulmonary disease), for the test to be considered adequate (details are provided in Table S2). Once the ventilator is reconnected, the patient should be briefly hyperventilated to correct for respiratory acidosis and to reduce the risk of hypotension.

ANCILLARY TESTING

The determination of brain death should be made on clinical grounds; ancillary testing should be conducted only when the clinical examination cannot be performed fully (e.g., in cases of severe facial trauma or swelling) or safely (e.g., apnea testing in a patient with hemodynamic or pulmonary instability). Although EEG was traditionally used in ancillary testing, its use has been deemphasized in more recent guidelines, largely owing to the low likelihood that electrical activity from the brainstem will be detected.[5,15] Even with concomitant use of evoked potentials to measure the electrical integrity of the brainstem, electrical testing is generally not considered to be useful in determining brain death, given risks of both false positive and false negative results.[16-18]

Testing of cerebral perfusion is the preferred method of ancillary testing; evidence of cerebral blood flow precludes a diagnosis of brain death (Table S3). Digital subtraction angiography (DSA) has long been used in the determination of brain death,[19] but it is labor intensive and associated with a risk of nephrotoxicity. Transcranial Doppler ultrasonography (Fig. S1) has also been accepted as a means of determining brain death and can be performed at the bedside, but its effectiveness depends on the ability of the operator, and in certain circumstances it is considered to be invalid (e.g., in patients with skull defects or ventriculostomy).[20] Alternatively, perfusion can be measured with the use of radionuclide angiography or perfusion scintigraphy (planar and single-photon-emission CT imaging), which have a specificity similar to that of DSA[21,22] (Fig. 3). These forms of imaging are best performed with the use of lipophilic agents, such as technetium-99m hexamethylpropyleneamine oxime, which can be used to evaluate both perfusion and the uptake of tracer by metabolically active cells. In contrast, lipophobic agents are useful only in the evaluation of perfusion.[23] Although numerous studies have supported the use of CT angiography,[24] magnetic resonance imaging (MRI), and magnetic resonance angiography,[25] these types of imaging have not been assessed in comparison with DSA and have been criticized for having unacceptably high false positive rates. Consequently, they are not currently recommended.[5]

DOCUMENTATION

Documentation should include full details of prerequisites and clinical examination, the names of examiners, and the results of laboratory tests, including the absence of confounding laboratory values and the values for the arterial blood gas before apnea testing has started and after the completion of the test. The time of death is typically the time at which the laboratory reports the values for arterial blood gas if the apnea test has been completed, or, if ancillary testing is

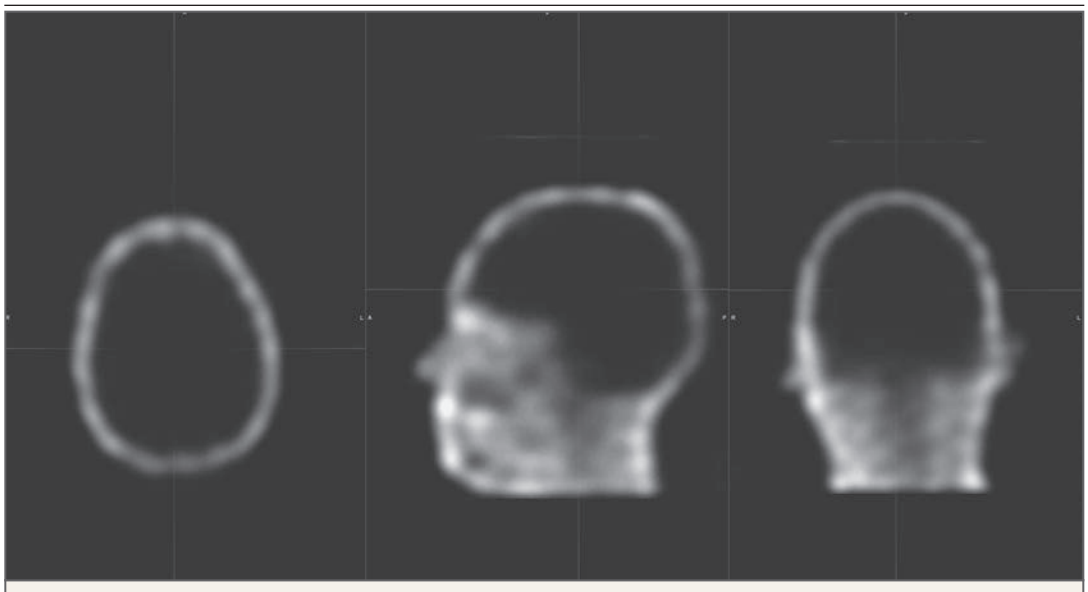

Figure 3. Single-Photon-Emission Computed Tomographic Image of the Brain, with Anterior–Posterior and Lateral Views.

It is imperative to obtain lateral views of the brain as well as anterior–posterior views after the presumed death of a patient to ensure that there is no uptake of tracer in the brainstem.

performed, the time at which the official report is signed. However, regulations may vary by state and hospital.

AREAS OF UNCERTAINTY

Determination of brain death is challenging in patients with hypothermia[5] or those requiring extracorporeal membrane oxygenation (ECMO).[5] Exposure to environmental hypothermia or therapeutic hypothermia in patients with cardiac arrest or, less commonly, those who require management of refractory elevated intracranial pressure may dictate a more prolonged waiting period (more than 24 hours) to ensure irreversibility on account of delayed neuronal recovery, drug metabolism, or both.[12] The concomitant use of cerebral metabolism–reducing agents such as pentobarbital may warrant a waiting period of several days (owing to its prolonged half-life) to ensure complete clearance. Clinical determination or, if needed, ancillary testing may be considered in these circumstances but only after standard neuroimaging (CT or MRI) has been performed and clearly shows a devastating cerebral insult consistent with cerebral circulatory arrest.

The use of ECMO has increased greatly in recent years, and a neurologic catastrophe can occur either during the primary event, necessitating the use of ECMO (e.g., cardiac arrest), or as a complication of ECMO (e.g., stroke). Testing for brain death can be performed in a patient who is receiving ECMO, but testing for apnea poses particular challenges.[5] Blood sampled from the distal arterial output provides an adequate approximation of blood gas levels in the cerebral circulation. Achieving the requisite rise in the partial pressure of carbon dioxide requires manipulation of the sweep gas flow rate (which determines the blood levels of both oxygen and carbon dioxide during ECMO) or titration of exogenous carbon dioxide into the ECMO circuit, mindful that acidosis is also an important stimulus during apnea testing (and its absence may lead to inadequate brainstem stimulation). The blood pressure must be maintained during testing, and given that many patients who require ECMO do not have pulsatile flow, a mean arterial pressure of at least 73 mm Hg in adults is probably appropriate (i.e., the equivalent of 100 mm Hg of systolic pressure and 60 mm Hg of diastolic pressure).

There is global variability with respect to the number and qualifications of examiners required, the mandatory waiting period, the details of

clinical evaluation, and approved forms of ancillary testing.[7] Studies are lacking to assess whether international guidance statements and training programs, including simulation[26] and online offerings,[27] will reduce the variability among countries and within the United States with respect to the determination of brain death. Prospective studies are needed to compare CT angiography and magnetic resonance angiography with other tests to assess perfusion and to determine adequate observation periods to ensure irreversibility for different conditions leading to brain death. Other controversies exist, and a detailed discussion of the ethical, legal, and religious issues is available elsewhere.

GUIDELINES

Guidelines for the determination of brain death have been published by the American Academy of Neurology (AAN) for use in adults (most recently 2010[11]; update in progress) and by several societies for use in children (2011).[9] Key differences between adult and pediatric guidelines include the number of assessments needed to determine brain death (one or two assessments in adults and two assessments in children), minimum temperatures for testing (36°C in adults and 35°C in children), and indications for ancillary testing (e.g., to shorten the waiting period between examinations in younger children). In 2020, the World Brain Death Project,[5] an international collaborative endorsed by 27 international societies, published comprehensive guidance regarding criteria for accurate determination of brain death in adults and children, including in special circumstances (e.g., hypothermia and ECMO), and guidance regarding the use of organ support for instances in which organ donation is planned. The present recommendations for determining brain death are consistent with this guidance.

A statement from the American College of Medical Toxicology stressed the importance of accounting for the residual pharmacologic effects in the determination of brain death after drug overdose.[28] The AAN also published a position statement regarding brain death in pregnancy, which included information on how to accommodate and communicate with families that are unaccepting of the concept or determination of brain death,[29] an increasingly frequent occurrence.

CONCLUSIONS AND RECOMMENDATIONS

In the patient described in the vignette, there is evidence of global anoxic injury on CT, with no brainstem reflexes or movement in his arms and legs in response to noxious stimulation other than bilateral triple flexion. These signs are spinally mediated, but careful attention is needed at the time of clinical examination to rule out any cerebrally mediated function. Before the determination of brain death, the persistent effect of any intoxicant needs to be excluded, especially given this patient's treatment with hypothermia. Although he is relatively young, secondary anoxic injury to his liver or kidneys may have compromised his ability to metabolize drugs. To be prudent, it would be appropriate to defer a definitive determination of brain death to the point beyond which the minimum half-lives of the drugs that the patient had received have elapsed, with a waiting period of 2 to 3 days from the time at which he became normothermic, during which time daily examinations should be conducted to look for any signs of brain function. Meanwhile, the patient should be stabilized with respect to metabolic and cardiopulmonary measures, after which a complete clinical examination and testing for apnea should be possible. It would also be useful to ask a colleague to perform a second, independent examination (as is required at my institution). Ancillary testing should be pursued only if conditions that may confound clinical assessments cannot be eliminated or hemodynamic stability cannot be achieved. Before the assessment of brain death is conducted, it would be important to have direct, compassionate conversations with the patient's family regarding the concept of brain death. Informed consent is not required before the determination of brain death, but careful navigation may be required to address cultural or religious objections, and in some instances ethical and legal consultation may be beneficial. Once brain death has been declared (but not earlier), it would be appropriate to speak with the family regarding the patient's wishes to donate organs to patients who might benefit.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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