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Neonatal Brain Death and Current Controversies: An Illustrative Case

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Abstract Brain death is a difficult determination, often involving legal, ethical, and moral dilemmas for care teams and families. Determination of brain death in the neonate is particularly difficult due to ambiguous and inconsistent guidelines, which have generated controversies and debates regarding several components of the brain death examination in neonates. The treatment team of a term neonate who suffered a severe hypoxic-ischemic brain injury during birth encountered numerous uncertainties as they navigated the brain death determination guidelines. This was the first time a neonatal brain death determination was performed at this 52-bed level III neonatal intensive care unit.

Keywords: *neonatology, brain death, hypoxic-ischemic encephalopathy*

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1. Introduction

What follows is a report of the first full-term neonate in the region to undergo brain death determination secondary to severe hypoxic-ischemic encephalopathy. This is followed by a discussion on current controversies over issues we encountered during the process. We end with a closing remark on the withdrawal of care in the neonatal intensive care unit (NICU).

2. Case Report

A baby boy weighing 3165 grams was born at 40 and 0/7 weeks gestation by emergent cesarean section (C-section) secondary to fetal decelerations to a 37-year-old G1P0 mother. The pregnancy was complicated by gestational hypertension, but the mother was otherwise compliant with prenatal care and maternal serologies were negative. The baby was hypotonic and apneic at birth with no heart rate or gag reflex and minimally reactive pupils. Aggressive resuscitation was initiated immediately after birth, and a heartbeat was detected at nine minutes of age. Apgar scores were 0, 1, and 1 at one, five, and ten minutes, respectively. The infant was intubated at 14 minutes of age. A complete neurological assessment at 90 minutes of age established the infant to be comatose with generalized hypotonia, absent deep tendon reflexes (DTRs), and absent Moro's, suck, and gag reflexes. The pupils were bilaterally dilated to five millimeters and nonresponsive to light.

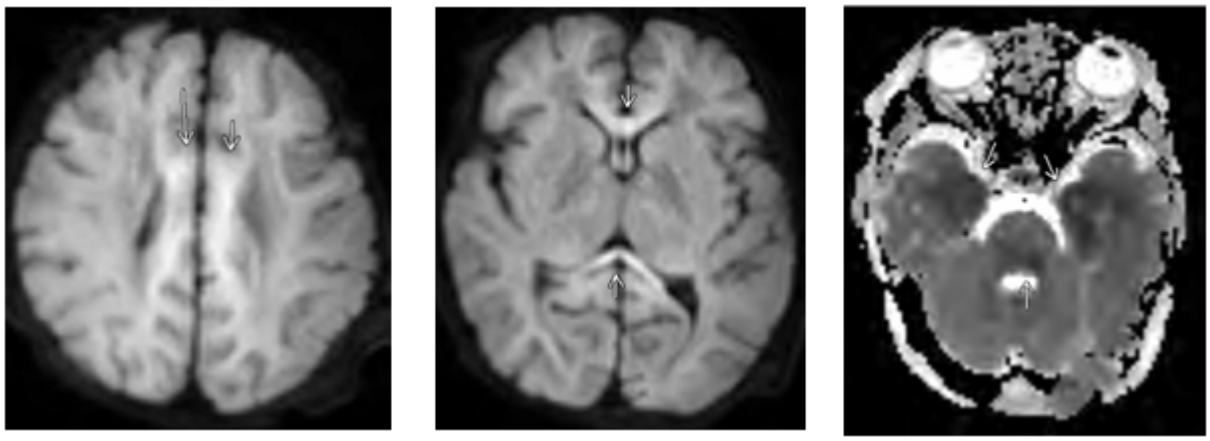

Figure 1. MRI demonstrating symmetric diffusion restriction of the corpus callosum, medial temporal lobes, and posterior pons

Therapeutic hypothermia was initiated at hour of life (HOL) 5. The infant underwent whole-body cooling for 72 hours according to the hospital's therapeutic hypothermia protocol. During the cooling period, a cranial ultrasound on the neonate's day of life (DOL) 2 was unremarkable. The infant was rewarmed on DOL 3 with no appreciative improvement to neurological status. An MRI was obtained on the day of rewarming and showed symmetric diffusion restriction involving the corpus callosum, medial temporal lobes, and posterior pons (Figure 1). There also appeared to be an abnormal FLAIR signal within the cortical/subcortical occipital regions. Collectively, these findings confirmed our suspicion of neonatal hypoxic-ischemic encephalopathy (HIE).

A video EEG placed on DOL 1 remained in place until DOL 6 and demonstrated findings consistent with severe global anoxic injury to the brain. Frequent focal seizures arising from the right frontal area correlated with fast shaking of the left arm (Figure 2). These ceased following the initiation of Keppra. Fosphenytoin was added following the emergence of left fronto-temporal and right fronto-centro-temporal epileptiform discharges on DOL 3. Throughout the study, the background remained severely suppressed.

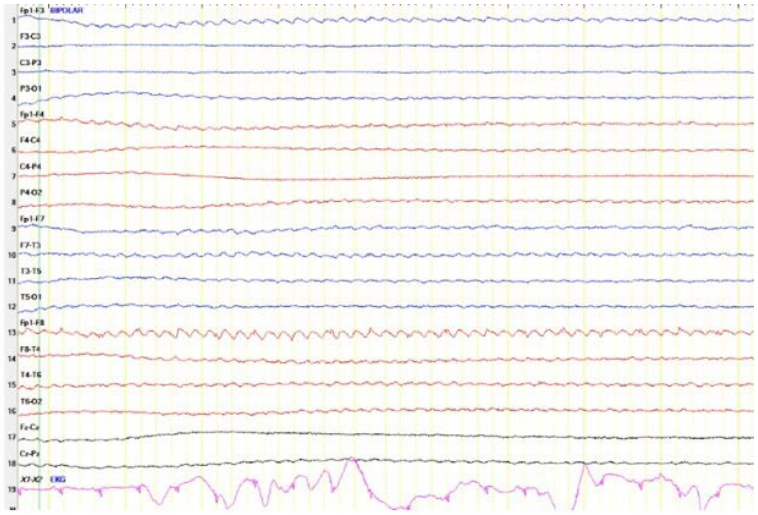

Figure 2. Sample of rhythmic R frontal 5 Hz activity which correlated with left arm twitching

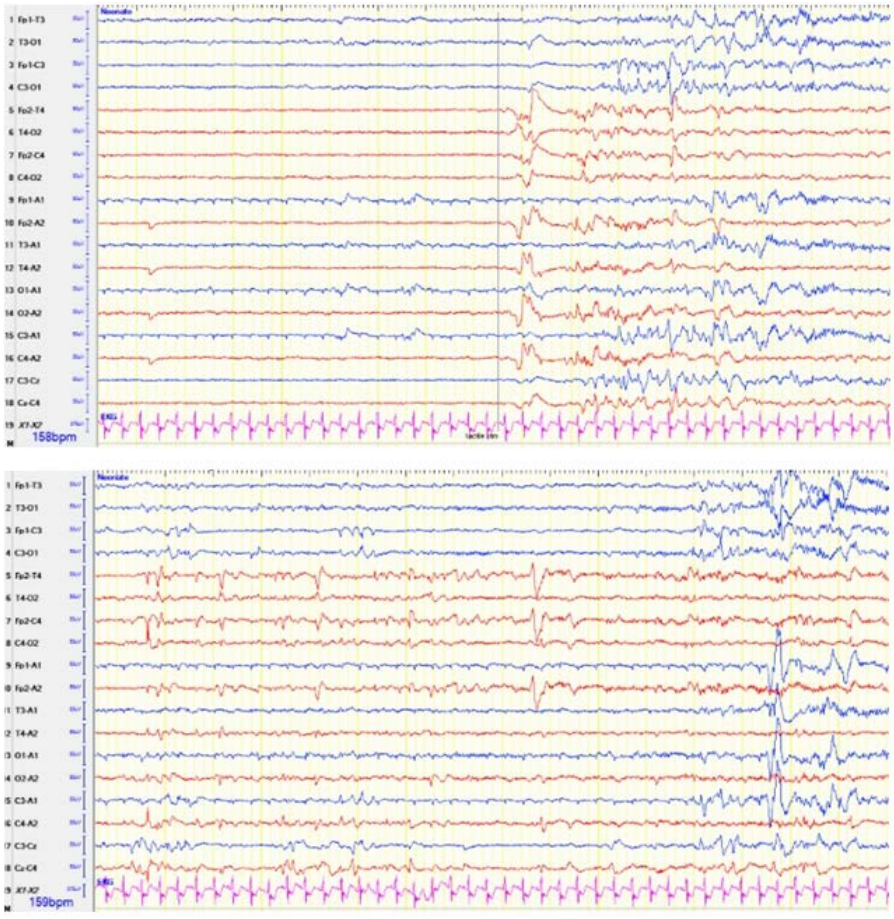

Figure 3. Ancillary EEG demonstrating cortical hyperexcitability during brain death determination

The infant's course was complicated by coagulopathy, thrombocytopenia, hyperglycemia, hyponatremia, hypomagnesemia, hypocalcemia, metabolic acidosis, and oliguria. These were all managed appropriately and normalized by DOL 7.

The infant's condition failed to improve, and a brain death examination was performed on DOL 7 in accordance with the American Neurological Association Guidelines for the Determination of Brain Death in Infants and Children, The American Academy of Pediatrics Guidelines for the Determination of Brain Death in Infants and Children, and The World Brain Death Project 2020 recommendations. The examination for brain death consisted of apnea testing and two neurologic examinations performed by different attending physicians, with each examination separated by a 24-hour observation period. The neonate failed the initial brain death testing on DOL 7 due to quick desaturations to the 50s during the apnea test, requiring the test to be terminated prematurely. The parents requested that the determination of brain death be attempted once more 2 to 3 days after the initial test and asked for the apnea test not to be repeated. For this reason, a bedside video EEG to assess for electrocerebral silence (ECS) was done as an ancillary test on DOL 9. This EEG was significant for frequent multifocal epileptiform discharges indicating underlying cortical hyperexcitability and potential epileptogenesis (Figure 3). With these findings, the infant was deemed not to meet the criteria for ECS.

After much discussion, the parents of the neonate decided that withdrawal of care was in the best interest of their son. Withdrawal of care took place on DOL 11. Intravenous fluids were discontinued, and the neonate was transferred to his father to hold while extubation took place. An assessment by the attending neonatologist confirmed absence of palpable peripheral pulses, no cardiac sounds on chest auscultation, and no spontaneous respiratory effort.

3. Discussion

Following the first successful defibrillation of a human heart in the mid-20th century and the widespread use of mechanical ventilation throughout the world, the number of "hopelessly unconscious" or "beyond coma" patients—patients that were neurologically devastated with absent respiratory effort and primitive reflexes—appeared in unprecedented numbers [1,2,3]. These patients only remained "alive" in the traditional sense because of the physiologic support offered by modern medicine. Medical professionals questioned if the determination of death should remain limited to the irreversible cessation of circulatory and respiratory function as had been the solitary definition of death for millennia.

In 1968 a second form of death—brain death (BD)—was defined by the Harvard Ad Hoc Committee. With this new definition, a person in an irreversible coma could now be considered dead [4]. This was followed in 1981 by the Uniform Determination of Death Act (UDDA) that established death could be declared by (1) "irreversible cessation of circulatory and respiratory function" or (2) "irreversible cessation of all functions of the entire brain, including the brainstem" [5]. Later, in 1987 a set of specific criteria for the diagnosis of BD in children was established. This set of criteria was most recently updated in 2011 by the American Academy of Pediatrics (AAP), the Society of Critical Care Medicine (SCCM), and the Child Neurology Society (CNS) [6].

In the United States, the ratio of infants (less than 30 days of age) declared BD compared to adults is 1:1000, with hypoxic-ischemic injury being the most common precipitant of BD [7]. Because BD in infants and children is a relatively rare occurrence, much of the evidence underlying the current guidelines for the determination of BD in this population is from case reports, case series, and limited studies [7]. Notably, these guidelines remain eminently similar to the guidelines used for adults.

The BD determination guidelines stipulate that to diagnose BD, physicians must first identify a mechanism of irreversible brain injury with confounders and mimicking conditions (such as electrolyte derangements, drug intoxication, and hypothermia) excluded. Second, children and infants must have two examinations with apnea testing separated by an observation period and performed by different physicians. For term neonates up to 30 days of age, the examinations should be separated by an observation period of 24 hours, but for children 30 days to 18 years of age, this observation period is shortened to 12 hours [6,7].

4. Brain Death and Its Controversies

The BD determination guidelines strive to denote a sharp boundary between life and death, but the legitimacy of BD determination remains a topic of contention. Decades since its legal indoctrination by the UDDA, physicians and families continue to encounter grey areas fraught with legal, ethical, and moral dilemmas—particularly in infants less than two months of age. Poor understanding and mixed interpretations of guidelines subject the medical community to confusion and indistinction in what is supposed to be an objective phenomenon. Major controversies and current debates surrounding the determination of BD are discussed below.

4.1. The Unique Nervous System of Neonates Requires Special Considerations

The clinical examination for BD determination relies heavily on testing the patient's brainstem reflexes. Some believe that applying the same criteria to neonates is foolish due to the immaturity of this population's reflexes [8]. The mandatory 24-hour observation period between clinical examinations is argued to account for this immaturity, with the second examination confirming an unchanged and irreversible absence of neurologic function [3,5,7]. Notably, however, this 24-hour observation period is arbitrarily defined. There are no studies on the appropriateness of this time duration nor on whether a longer or shorter observation period is more sensitive for BD determination in infants and children [7].

4.2. Apnea Testing

There is concern that the apnea test violates the ethical pillar of non-maleficence [3]. Apnea testing, which involves pre-oxygenating the patient and then disconnecting them from the ventilator, is consistent with BD when the patient fails to breathe spontaneously after the arterial carbon dioxide ($PaCO_2$) concentration rises above 60 and 20 mm Hg above the pre-test baseline [7]. The resulting acidosis from the rise in $PaCO_2$ can cause hemodynamic instability, cardiac dysrhythmias, and cerebral herniation [3,8,9]. Despite these concerns, the inclusion of apnea testing remains in the current guidelines for neonatal determination of BD. In the event that the patient does suffer severe cardiopulmonary dysfunction during the apnea test, ancillary testing, which is discussed next, is utilized to aid in the diagnosis of BD.

4.3. Ancillary Testing

Pediatric guidelines permit the use of ancillary testing to 'complement' the clinical examination in certain situations where a complete clinical exam and apnea test cannot be completed [7]. Permissible ancillary testing in the pediatric population includes EEG and radionucleotide cerebral blood flow (CBF). Both of these tests, however, are less sensitive in newborns compared to infants older than 30 days of age [7,8].

CBF studies may be inappropriate ancillary tests for neonates. In this very young age group, there can be the persistence of blood flow in the context of BD secondary to the open sutures/fontanels of infants allowing for less significant intracranial pressure (ICP) increases. When ICP is kept to a minimum, it follows that CBF is able to persist. Some are of the opinion that CBF testing is not sufficiently robust to aid in confidently diagnosing BD in infants less than 2 months of age and, therefore, should not be used to assist in BD determination for this age group [10].

EEG may also be a poor ancillary study to assist in BD determination as it cannot verify brainstem function cessation. The diagnosis of BD is considered when the absence of electrical activity, known as electrocerebral silence (ECS) or electrocerebral inactivity (ECI), is maintained on EEG for at least 30 minutes (drugs, hypothermia, and other potential causes of cerebral activity depression must not be present) [11]. However, patients with ECS on their EEG may have normal brainstem function [8]. Therefore, the irreversible cessation of the entire brain, which mandates the inclusion of the brainstem (whole-brain death), cannot be adequately determined.

EEG as an ancillary test has also generated debates over the presence of nonconvulsive seizures. In the current guidelines, nonconvulsive seizures are not explicitly stated as a confounding factor. Proponents in support of this argue that nonconvulsive seizures cannot mimic all of the findings of BD [12]. Those against contend that the AAP guideline stating that confounding factors are those "factors potentially influencing the neurological examination" should be interpreted as "disorders that can influence any component of the clinical examination are confounding factors." If this side of the argument is taken, then a confounding factor must only account for *one* of the findings of BD [13]. Thus, the presence of nonconvulsive seizures, which can cause coma, loss of cough and gag reflex, or apnea, would prohibit a BD diagnosis. It should be noted, however, that some EEG activity (minimum or transient) may be considered an artifact, as demonstrated by case reports of BD infants with brain function preservation who ultimately died or survived with severe neurological complications [8].

4.4. Should BD Determination Require the Irreversible Cessation of All Functions?

In a similar vein as the EEG debate, the irreversible cessation of *all* functions as a requirement for BD determination is often debated. In fact, this criterion is not universally accepted, with the definition of BD varying depending on the country. In the United States, New Zealand, and Australia, a *whole* brain death definition is used. *Whole* BD requires the irreversible cessation of all clinical functions of the brain, including the brainstem. In other parts of the world, such as the United Kingdom, India, and Canada, a *brainstem* death, which is the cessation of functions of the brainstem only rather than the whole brain, establishes the diagnosis of BD [3,7]. The overarching concept of BD, however, remains the same—BD is a clinical diagnosis based on the absence of neurological function with a known cause that has resulted in an irreversible coma.

5. Forgoing Life-sustaining Medical Treatment

Neonatal BD determination is a difficult task filled with non-universal, nebulous guidelines that incur minor but important differences in interpretation. In our situation, we were not able to confidently declare BD due to a failed apnea test and uncertainty on whether or not the neonate met BD qualifications on ancillary EEG testing. This left the infant's family and treatment team with another ethical, moral, and legal dilemma: is it ethically advisable to sustain the child's life, or is the withdrawal of interventions appropriate?

Decision-making regarding providing or forgoing life-sustaining medical treatment (LMST) is guided by the patient's best interest, but few standards exist for neonatal palliative care [14,15]. Often the approach of "provisional intensive care" is done. This is a time-limited trial of LSMT that is withdrawn after a lack of improvement in the patient's status following a prespecified period of time [14]. Decisions to forgo LSMT in neonates may be exceptionally difficult because of the uncertainty about prognosis [15].

In the care of newborn infants whose prognosis is very poor and survival may be associated with diminished quality of life, the AAP affirms that "parental desires should determine the treatment approach." The AAP also considers treatment "inappropriate" and favors withdrawal

of LSMT when it is "harmful, of no benefit, or futile and merely prolonging dying" [14]. Similarly, the United States Congress established in 1994 that withholding treatment from infants is considered child abuse except when (1) an infant is chronically and irreversibly comatose; (2) when providing treatment would only prolong dying, would not ameliorate or correct the infant's life-threatening condition, or would be futile in terms of the infant's survival; or (3) when the treatment would be inhumane [14].

More than 80% of the deaths in the neonatal ICU are preceded by a decision to withdraw or withhold care [15]. The discontinuation of interventions that sustain oxygenation and tissue perfusion in a child who does not meet neurological criteria for BD (despite having an irreversible and devastating neurological injury) will die under the original definition of death—that is, circulatory death.

6. Conclusion

The ability to sustain cardiopulmonary function and other advancements in medical technology introduced a second legal definition of death in the form of BD. The determination of BD, particularly in the neonatal ICU, remains a source of controversy and debate, causing inconsistencies and physician confusion on the boundary between life and death. This is particularly true for care teams performing the examination for the first time at institutions unfamiliar with neonatal BD determination. A resolution of the controversies surrounding apnea testing and the applicability of ancillary testing would allow for the establishment of clear and universal guidelines for determining BD in neonates.

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Declaration of Interests

The author declares that there is no conflict of interest.

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