Is brain death diagnosis in newborns feasible?
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Abstract
Brain death as the irreversible and permanent loss of cerebral and brainstem function, is relatively uncommon among newborns who need life support. It is considered the result of an acute and irreversible central nervous system insult. Asphyxia, severe intracranial hemorrhage and infection are the most common causes of brain death in children. BD diagnosis is usually based on clinical criteria. Because of major differences of brain function in this age group, brain death should be established with extreme caution. Comparative to adults’ longer observational periods (at least 24 hours apart) and specific neurodiagnostic tests, by at least two expert physicians, are needed to ascertain an irreversible loss of brain function. The objective of this article is to present current guidelines for BD determination in newborns and to refer their application in Greece.

Key Words: Brain death, electroencephalography, cerebral blood flow, newborn

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Introduction
Brain death (BD) is the permanent and irreversible loss of brain stem, neocortical and whole brain death are not identical. Loss of brain function, arises medical, ethical and philosophical issues. Loss of brain function is also loss of human life, even though heart and spinal cord may still operate. Development of cardiorespiratory support in neonatal intensive care units (NICU’s), arouse the need to define BD criteria in newborns. BD diagnosis is vital for parents and medical staff to help them decide if a newborn should be supported further or not.

BD criteria in adults can be implemented for children, infants, full-term newborns (except for premature newborns < 37 weeks gestational age because of insufficient data) despite differences in brain function assessment, resistance to hypoxia and aetiology of BD as well. Guidelines from repeated task forces emphasized the importance of medical history/clinical examination in determining the aetiology and irreversibility of coma, specifying age - observational periods and ancillary neurodiagnostic testing. Determination of brain death in newborns is based mainly on clinically accepted neurologic criteria. Age related observational periods and the need for neurodiagnostic tests are still needed to be evaluated for BD diagnosis in children under 1 year of age. Considering variation for BD diagnosis guidelines in children from country to country, these have not been clearly established in Greece. This review discusses current accepted definition, diagnosis and appropriate testing for brain death in newborns.

Epidemiology
In neonatal units, the percentage of BD among deaths has been found 1–6.3%. BD newborns are comatose, apneic with their brainstem reflexes absent. It is of great importance to confirm BD in newborns with serial clinical neurologic examinations and ancillary tests.

Definition
BD criteria for infants <2 months remain controversial while in older children and adults have been well established. Harvard Committee in 1968 and Medical Consultants Report in 1981 established guidelines for the determination of BD in adults based on neurologic criteria. In 1987, the American Task Force for the Determination of BD in children, established guidelines in the age group under 7 years old, while preterm and term infants under 7 days old were excluded because of insufficient data. In 1991 a report of a Working Party of the British Paediatric Association recommended that the criteria used for adults can only be applied in children over the age of two months. Recent studies suggest that BD criteria in infants under 2 months of age can also be used for preterm and term infants within the first week of life. 1987’s BD guidelines for children younger than 1 year of age in United States, were recently revised in 2011 by Nakagawa et al. These guidelines are based in definition of coma cause, irreversible cessation of entire brain’s function (specifically brain stem), exclusion of reversible causes, clinical neurological examination criteria, neurodiagnostic tests and suggestion of specific observational periods according to age (Table 1).
Table 1: Brain death guidelines in children (modified form from Ad Hoc Task Force guidelines for the determination of brain death in children).8

<table>
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<th>History</th>
<th>Determination of coma cause and exclusion of reversible causes (hypothermia &lt;35º, hypotension/shock, drug intoxication, i.e. barbiturates, sedatives, hypnotics, narcotic analgetics, neuromuscular blocking agents)</th>
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| Physical examination | • Coma and apnoea. No movements such as seizures, dyskinetic movements, decorticate/decerebrate movements are present except activity mediated at spinal cord level  
  • Absent brainstem function reflexes  
  a. mid position or fully dilated pupils  
  b. absent oculocephalic (‘doll’s eye’) movement,  
  c. absent caloric-induced eye (‘vestibulo-ocular’) movement  
  d. absent corneal, gag, cough, suck and root reflexes  
  • Absent respiratory movement with apnea testing  
  • Consistent examination findings throughout a predetermined period |
| Suggested period and investigation according for term newborns (>37 weeks GA) to 30 days age | • 2 different physicians should perform 2 clinical examinations each, following an observational period of 24 hours. Waiting period of 24 hours for clinical examination is suggested after a severe brain insult or cardiopulmonary resuscitation.  
  • Ancillary tests are not required except in cases where the clinical examination and apnea test cannot be completed.  
  • Observational 24h period could be reduced if EEG/CBF study are confirmatory of BD diagnosis. |

Diagnosis

Brain dead patients supported on mechanical ventilation, are comatose, apneic and lack brain stem reflexes. BD diagnosis requires clarification of: Etiology, clinical examination, apnea and ancillary testing. Before determination for BD diagnosis, reversible conditions such as hypothermia, fluid and electrolyte abnormalities, altered metabolic status, hypotension, surgically curable conditions and exposure to toxins / medications should be treated and excluded.8,18. Common causes of BD in neonates are perinatal asphyxia, birth trauma, central nervous system (CNS) infection, malformations, severe intracranial hemorrhage (intraventricular hemorrhage grade IV) and metabolic diseases.8

Neurologic examination remains the cornerstone for determination of BD.19. Assessment of an unresponsive/unresponsive infant in coma with lack of consciousness can be sufficiently performed with tactile, visual and auditory stimulation.19. Loss of brainstem function can be assessed by testing pupillary reactivity (absent prior to 30-32 weeks’ gestation), ocular motility [oculocephalic / oculovestibular reflex] (absent prior to 32 weeks’ gestation), corneal and gag reflex. Grimacing or motor response (withdrawal movements) to stimuli or in response to brainstem reflexes excludes BD diagnosis. Inability to apply clinical criteria e.g. trauma to the eyes, ear injuries, cranial neuropathies, metabolic/endocrine disturbances, dehydration should be taken under consideration for a proper clinical examination. Revised guidelines of 1987 guidelines by Nakamoto et al suggest that BD cannot be diagnosed in preterm newborns (<37 weeks GA) because of the difficulty to assess adequately the level of consciousness and brainstem function in this age group.8 Apnea testing after disconnection from the ventilator by measuring pCO2 levels > 60mmHg or > 20mmHg above baseline values (at 5 min intervals for 15mins maximum), that detects chest wall movement can be used additionally for BD diagnosis. Euvolemia, normal blood pressure, normal pCO2, and preoxygenation for 5-10 minutes are prerequisites for an appropriate apnea test.19,20

Neurodiagnostic ancillary tests offer information for whole brain death and regarding the key role of brain stem function in BD diagnosis should be used under certain conditions. Ancillary tests are required when neurologic examination cannot be evaluated reliably (i.e. severe neuromuscular or lung disease, hypotension), an incomplete apnea test, when a medication effect is still present and to reduce the observational period.8,19-22. In newborns BD diagnosis is based on clinical criteria (confirming brain stem diagnosis) but also on neurodiagnostic tests (electrophysiologic / brain blood flow) detecting brain stem and whole brain death as well.23

Neurodiagnostic electrophysiologic tests [electroencephalography (EEG), brainstem auditory evoked potentials (BAEPs), somatosensory evoked potentials (SEPs)] can assess brain electrical activity. EEG’s role in determining BD diagnosis is controversial since it cannot record brainstem function cessation. Patients with electrocerebral silence (ECS) on their EEG may have normal brainstem function and vice-versa in BD patients with loss of brain function, cortical activity (even transitory) may be traced. Thereby, EEG has been found isoelectric in 51-100 % of BD neonates or even normal.21,18 Absence
of electrical activity (ECS) for at least 30 minutes on the initial EEG supports the diagnosis of brain death. ECS on the first EEG study that remains isoelectric on a repeat study or normal EEG on the first study that is followed by ECS on a second study confirms BD diagnosis. These data reveal that only one, unchanged EEG with ECS and the newborn’s examination remains unchanged for 24 hours, is confirmatory of BD. Drugs that cause reversible loss of EEG activity are phenobarbital (>25 μg/mL), benzodiazepines, narcotics and intravenous (thiopental, ketamine, midazolam) anesthetics. ECS in the absence of drugs, hypothermia, CNS malformations with constant clinical findings for 24 hours establishes BD diagnosis. However ECS on EEG, is not always confirmative for BD diagnosis. Published case reports have shown preservation or recovery of brain function after a period of time in brain dead infants with with some degree of EEG activity (minimum or transient EEG). Most infants died within a short period of time while those who survived recovered with severe neurologic complications. In this case, EEG activity is considered an artifact and for BD diagnosis additional testing is needed. Likewise, in newborns once the diagnosis of BD is established recovery is unlikely to happen, since there are no reports of any newborn that developed respiratory effort after brain death determination. Brain blood flow tests [radionuclide angiography, digital subtraction angiography] are invaluable to confirm BD diagnosis. No detection of flow on cerebral blood flow (CBF) study was observed in 58-72% of BD neonates. Preservation of blood flow in BD neonates’ brain is explained by less significant intracranial pressure increases because of open sutures/fontanels. Evidence of low cerebral blood flow, with a repeat no flow on CBF study after, establishes diagnosis of BD. No flow on CBF study with ECS on EEG definitely confirms BD. However, evidence of blood flow on a CBF study with ECS should alert the physician to search for causes of reversible EEG activity loss, as mentioned previously. Recent data for newborns conclude that EEG with ECS is less sensitive (30%) than no flow CBF study (63%), for BD diagnosis. These data suggest that the attending physician, who establishes a BD diagnosis, should estimate findings from EEG and CBF study very carefully. Neurodiagnostic neurophysiologic tests [brainstem auditory evoked potentials (BAEPs), somatosensory evoked potentials (SEPs)], brain perfusion tests [transcranial Doppler ultrasonography, CT/MRI angiography] and imaging [CT/MRI] have also been used for BD determination but still remain to be evaluated in newborns. Two clinical examinations separated by an observational period of 24 hours for term newborns (37 weeks GA) to 30 days of age by two expert medical practitioners (one should be a pediatrician consultant registered for more than 5 years and one who’s not primarily involved in the newborn’s care) are required to establish BD diagnosis. The importance of defining a certain observation time and the presence of experienced physicians is based on the need to re-evaluate the nonfunctioning brain and reduce the possibility of an error.

Ancillary tests for children < 1 yr of age, may be used to shorten interval periods of observation. Consequently, the observational period for BD diagnosis at terms, from 24 hours could be reduced when an isoelectric EEG or a no flow on a CBF study is established. If an EEG confirms some degree of activity or a CBF study shows evidence of flow it is recommended a repeat clinical examination rather than an ancillary test, confirming BD diagnosis after a 24 hours observational period.

Greece has passed a law since 1985 for the determination of BD in children >2 months. NICU’s policy for BD diagnosis in newborns is not based to a specific checklist, because of lack of certain guidelines. New guidelines for BD in newborns should be established and implemented on a national basis.

Conclusions
BD criteria for newborns and adults have a common basis despite different central nervous system pathology (immaturity of reflexes, open sutures/fontanels and intracranial pressure changes). BD should be based mainly on neurological clinical examination and ancillary testing. Combination of neurologic examination, ECS and no flow on CBF study in a preterm or term newborn for 24 hours observational period is confirmatory of BD. BD diagnosis helps parents and medical staff to realize newborns’ condition. Medical staff should always support and help parents in every decision they’ll take (dis- or continuation of life support) based on a mixture of sensitivity and factuality.

Conflict of interest
The authors declare no conflicts of interest.

References


