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Brain Death in Pediatric Patients in Japan: Diagnosis and Unresolved Issues

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Abstract

Brain death (BD) is a physiological state defined as complete and irreversible loss of brain function. Organ transplantation from a patient with BD is controversial in Japan because there are two classifications of BD: legal BD in which the organs can be donated and general BD in which the organs cannot be donated. The significance of BD in the terminal phase remains in the realm of scientific debate. As indicated by the increasing number of organ transplants from brain-dead donors, certain clinical diagnosis for determining BD in adults is becoming established. However, regardless of whether or not organ transplantation is involved, there are many unresolved issues regarding BD in children. Here, we will discuss the historical background of BD determination in children, pediatric emergencies and BD, and unresolved issues related to pediatric BD.

Key words: brain death, medical ethics, organ transplantation, pediatrics, Japan

Introduction

Brain death (BD) is a physiological state defined as a complete and irreversible loss of brain function. However, a social consensus has not yet been reached regarding whether or not BD can be considered to be human death in Japan. Because of the mistrusted event in the first heart transplant surgery in Japan, which was held in 1968, historically, a debate regarding BD in Japan has been strongly linked to organ transplantation, and the significance of BD in the terminal phase of neurological diseases has remained not only a topic of scientific debate but also an unresolved ethical issue. Due to the longevity of this debate, Japan's progress with organ transplantation legislation was delayed and the first organ transplantation from a brain-dead donor was performed in 1999, 30 years after the first unsuccessful experience. The Japanese Organ Transplantation Law[1)] states that legal BD is considered human death when organs will be donated. Conversely, following a diagnosis of general BD, organs are not to be donated. General BD does not signify the time of death, and therefore, no declaration of death shall be made. Hence, there is a double standard regarding organ donation for these two types of patients with BD[2)] (Fig. 1).

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In the past, related academic societies have independently made statements regarding the general significance of a diagnosis of BD, and the following proposal was made in 1998 by the Japan Neurosurgical Society:

> "[…] the determination of BD is an important basic part of medical practice for grasping status and determining prognosis that should be based on sufficient understanding of the family of the patient after the medical team gives them an appropriate explanation. In addition, if BD is determined with an appropriate procedure, the medical team manages the issue regarding the subsequent treatment, taking the patient's living will and wishes of their family into consideration. The Japan Neurosurgical Society considers it vital that the important medical practice of BD determination continues not to be subject to restrictions in the future […]." [3)]

In 2006, in a document titled "Proposal for views on determining BD and treatment after determining BD," the Japan Association for Acute Medicine stated that "BD is human death and is a medical phenomenon that is unrelated to social and ethical issues."[4)]

In 2015, the organ donation system maintenance committee of the Japan Council of Organ Transplantation Related Academic Societies (JCOTRAS) stated that "knowledge and technical perspective of clinical neurology, electrophysiology, and neurocritical care are required for definite diagnosis of brain death.

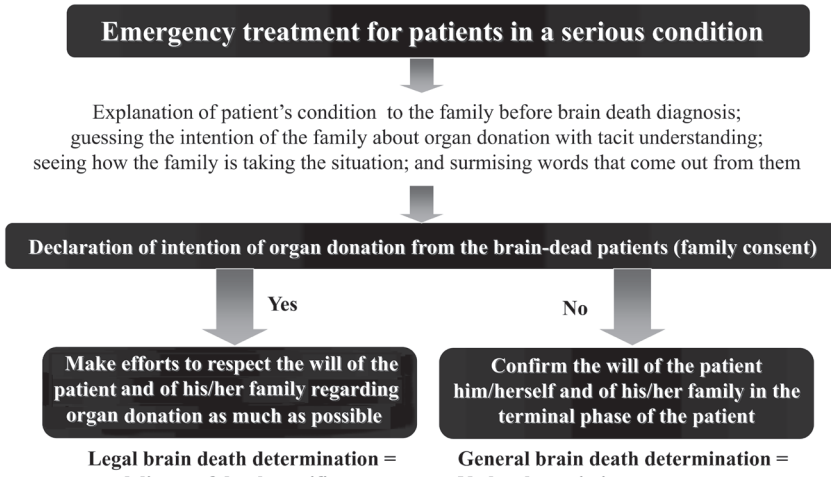

Fig. 1 The significance of brain death diagnosis in Japan.

Moreover, all healthcare providers must be carefully considerate toward patients who were diagnosed with brain death and their family."[5] This article discussed the historical background of pediatric BD determination, pediatric emergencies and BD, and unresolved issues related to pediatric BD.

Historical Background of Pediatric BD Determination

The Harvard criteria excluded children under 6 years of age from being subject to BD determination.[6] In 1987, a council of the related academic societies of the United States published guidelines for the determination of BD in children.[7] However, the need for a revision of these guidelines has arisen for the following reasons: (1) low absolute number of pediatric BD cases, (2) inconsistent sensitivity and specificity of ancillary tests, (3) unclear medical foundations for establishing age-specific criteria, (4) lack of BD determination criteria for neonates, and (5) accumulation of problems such as chronic BD. In the United States, there is no legal obligation requiring the use of nationally unified BD determination criteria, and there is a significant variation among facilities as to who makes the judgment, how long the judgment intervals should be, and whether apnea testing should be performed. As a result, questions have arisen pertaining to the quality of BD determination.[8] In 2006, the guidelines for the determination of BD in children were established in Canada;[9] and in 2009, the American Academy of Neurology revised the criteria for BD determination in adults[10] based on the concept of the Uniform Determination of Death Act in the United States. Following this, the criteria for BD determination in children were also revised[10] in 2011 for the first time in 25 years.

The BD determination criteria (Takeuchi criteria) proposed by the Japanese Ministry of Health and Welfare [MHW; called the Japanese Ministry of Health, Labour and Welfare (MHLW) in 2001] also excludes children under 6 years of age from being subjected to BD determination. In 1999, the MHW established a research group for BD determination criteria in children. In 2000, the results of a "Fact-finding survey on pediatric BD" and "Criteria for the determination of BD in children" with an adjusted age of 12 weeks or older were published.[11] These determination criteria were based on the Takeuchi criteria, and the exclusion criteria for the adjusted age was stipulated to be 12 weeks and under as an item specific to children. Additional requirements included the following: (1) the judgment interval for BD determination shall be extended to at least 24 h if the patient is under 6 years of age, (2) the minimum body temperature for hypothermia shall be 35°C, and (3) diagnostic imaging (computed tomography; CT) shall be used for the diagnosis of the underlying disease.

Under previous Japanese laws, it was considered problematic that the number of brain-dead donors undergoing organ donation had remained extremely low among developed countries and that organ donation from children below 15 years of age had been restricted. In 2003, the Japan Pediatric Society Ethical Review Board and the Board for Investigation of Organ Donation from Pediatric Brain-Dead Donors urged that with respect to the problems surrounding BD in children, "the rights of the children who are to be donors and recipients must not be infringed upon" and requested (1) expression of

- **1985: The Ministry of Health, Labour and Welfare's Special Scientific Study Project, "Brain Death Research Group" for Standard Brain Death Determination Criteria" (Takeuchi criteria)**
- **1999: Research group for brain death determination criteria in children**
- **2000: Brain Death Determination Criteria for Children (The Journal of the Japan Medical Association: 124/11)**
  - **Based on Takeuchi criteria**
  - **Infants under adjusted age of 12 weeks excluded**
  - **Determination interval time: 24 h for children under 6 years of age**
  - **Computed tomography used to diagnose underlying diseases**
- **2003: Recommendation by Japan Pediatric Society's Ethics Review Committee**
  - **Expression of patient's own intention**
  - **Training of coordinators specializing in pediatric organ transplantation**
  - **Avoidance of organ donation from brain-dead abused children**
- **2008: The WHO Istanbul Declaration**

Fig. 2 Historical background of determination of brain death in Japan.

self-intention, (2) training of coordinators specializing in pediatric organ transplantation, and (3) establishment of policies to avoid organ donation from brain-dead abused children.[12] In 2008, the Declaration of Istanbul, which recommended the restriction of transplant tourism and self-supply of organs, was adopted. After many discussions, the revised organ transplant law was established in 2009 (Fig. 2). With respect to the determination of legal BD for children in particular, "the exclusion of abused children" gained attention.[1,13] As of December 2014, organs have been donated by two brain-dead children below 6 years of age. In 2009, MHLW's special scientific study project "Research Regarding Determination of BD in Children and Organ Donation" was written as the basic guideline for maintaining this system and reported on the following: (1) criteria for pediatric BD determination,[13] (2) facilities for organ donation by brain-dead children,[14] and (3) the role of cerebral blood flow (CBF) testing in BD determination.[15] Each of these three items is described in detail below. A legal BD determination manual was later compiled.

Criteria for Determining Legal BD in Children

I. Outline of determination criteria for pediatric BD[13]

Legal BD determination is conducted on children aged 12 weeks or older and younger than 6 years using pediatric BD determination criteria. (For children born before 40 weeks' gestation, 12 weeks or older is calculated from the due date of their birth.) For children aged 6 years or older, the Takeuchi criteria are used. The preconditions state that magnetic resonance imaging (MRI) may be considered as a form of diagnostic imaging necessary for a "definitive diagnosis of the underlying disease." Cases that shall be excluded include abused children; children with hypothermia, metabolic disorders, or endocrine diseases; and those affected by drugs. For "vital sign confirmation," hypothermia shall be 35°C or below for children with an adjusted age of 12 weeks to below 6 years. In addition, criteria were established to determine blood pressure disproportionate for the child's age. Furthermore, the volume of ice-water injection (25 ml) for the vestibular reflex, judgment interval (at least 5 min), and methods for brain wave measurement and apnea testing were changed slightly (Fig. 3).

II. Facilities and physicians' qualification for the determination of BD[14]

The determination of BD in children has conventionally been conducted in four major types of hospitals: university-affiliated hospitals, facilities with medical advisers designated by the Japanese Association for Acute Medicine, basic or training facilities of the Japan Neurosurgical Society, and emergency and critical care centers. However, facilities that are members of the Japanese Association of Children's Hospitals and Related Institutions have been newly added as the fifth type of facility. In addition, the determination of legal BD in children shall be conducted by at least two physicians, including neurosurgeons, neurologists, emergency physicians, anesthesiologists, resuscitologists, intensive care physicians, or pediatricians, who are selected by the ethical review board or a similar body within the providing facility, have a qualification from the relevant specialized academic society, are society-certified physicians, have a wealth of experience in determining BD, and are not involved in organ transplantation.

Legal Brain Death Determination Manual (Ministry of Health, Labour and Welfare Special Research Grant, Health Labour and Sciences Research Project, "Research Group for Making a Manual for Brain Death Determination Standards" 2010 Report) shall be followed to determine brain death.

Age	Exclude infants under 12 weeks (for infants born before 40 weeks' gestation, 12 weeks from the due date)
Body temperature	Exclude if core temperature (ex. rectal, esophageal) is below 35°C (under 6 years old)
Measurement interval	24 hours or longer (under 6 years old)
Systolic blood pressure	65 mmHg or higher (under 1 year old) (age ×2)+65 mmHg or higher (1 year or older, under 13 years old) 90 mmHg or higher (13 years or older)
Brain waves	At least 5 cm between electrodes is recommended (infants)
Vestibular reflex	25 mL of ice water shall be injected (under 6 years old)
Apnea test	Methods include using T-beads and flush with 6 L/min of 100% oxygen (under 6 years old)

Fig. 3 Legal pediatric brain death determination. The Legal Brain Death Determination Manual (Ministry of Health, Labour and Welfare Special Research Grant, Health Labour and Sciences Research Project, "Research Group for Making a Manual for Brain Death Determination Standards" 2010 Report) shall be followed to determine brain death.

III. CBF testing in BD diagnosis[15]

CBF testing, with single photon emission computed tomography (SPECT), CT perfusion images, and MRI perfusion images offers sufficient precision as ancillary testing for legal BD determination. SPECT can diagnose 1% of residual normal blood flow, whereas CT and MRI, 2.5%. CBF testing offers various levels of sensitivity for BD diagnosis but has little significance as "absolute" testing.

IV. Exclusion of abused children from organ donation

Article 5 of the revised organ transplant law states that "[t]o prevent the donation of organs from children who have died after suffering from abuse, persons involved in organ transplantation must confirm whether there is a suspicion that the said child suffered abuse, and if there is a suspicion, they must treat the child appropriately." (2009)

In October 2010, a questionnaire survey regarding the system for organ donations from brain-dead donors was conducted on section A (385 facilities) and section C (739 facilities), which were all the Japan Neurosurgical Society neurosurgeon-training facilities. Thirty-nine section A facilities (17%) answered that an organ donation system for children was maintained. Many of the facilities that answered no to this question had "no framework for pediatric BD determination of or response to abuse" or lacked the ability to respond to abuse cases.

Essentially, abused children are not to be diagnosed for the aim of organ donation but as part of routine medical practice; therefore, a framework for the detection of any kind of abuse cases should not be prepared to enable organ donation from brain-dead donors. It has also been indicated that when responding to cases of past abuse, the prompt response to requests for the disclosure of information from child consultation centers is strongly encouraged.

The prohibition of organ donation from abused children is a rule that is only enforced in Japan. Furthermore, many physicians in Japan are also of the opinion that the requirement to investigate past instances of abuse places a heavy burden on those in medical practice. Currently, if there is even a slight suspicion of abuse, legal BD will not be determined. Moreover, regardless of whether a child suffered BD or cardiac death, organs will not be donated if there is a suspicion that they were the victim of abuse. However, even children who suffer severe brain damage due to abuse may exhibit cerebral herniation. In such cases, if an irreversible arrest of all brain functions, including the brainstem is observed, then the patient may be diagnosed as medically brain dead. However, in such a case, a declaration of death cannot be made with this determination of BD.

Pediatric Emergencies and BD

The results of a survey performed in North America regarding the epidemiology of pediatric BD serve as

a reference for pediatric emergencies and BD. It was found that head injuries due to traffic accidents or abuse are the most common underlying diseases in cases of BD. These are followed by drowning, asphyxiation, and hypoxic encephalopathy due to sudden infant death syndrome (SIDS). Extensive central nervous system infection may also destroy brain tissue.

Joffe et al.[16] reported 135 cases of BD in a 4-year investigation of a pediatric intensive care unit (PICU) in Canada. BD accounted for approximately 15% of all mortality cases, and the most common underlying disease was head injury, accounting for 44% of the cases. BD was determined on two separate occasions in 110 of 135 (81%) of the patients; 60 of these 110 patients (55%) donated organs. BD was determined once in the rest of 25 patients (19%) BD determination was not done in seven of these patients because of unstable hemodynamics. The families of 12 of these 25 patients offered organ donation, and 3 patients donated organs after being determined as brain dead once. Two of these patients were determined as brain dead based on CBF testing, and one patient donated organs without undergoing ancillary testing.

Pereyra et al.[17] retrospectively investigated whether decompressive craniectomy for severe cranial injury affected the occurrence of BD. They found that of the 698 patients examined, BD occurred in 108 patients (40 did not meet all BD criteria; mean BD occurrence rate, 16%); and they concluded that decompressive craniectomy was ineffective in preventing BD.

Sánchez-Olmedo et al.[18] reported that of 404 cases of severe cranial injury, 59 with a combination of hypoxia and hypotension (14.6%) suffered BD. They concluded that because secondary brain damage was strongly involved in BD onset, its prevention is crucial.

The epidemiology data in Japan was derived mainly from the MHLW study project for BD determination criteria in children. Of the 139 subjects, 79 suffered BD due to primary brain damage, and 60 suffered BD due to secondary brain damage accompanying asphyxiation or drowning. Cranial injury was the most common cause of BD due to primary brain damage (49%). Many cranial injuries were observed in male child patients.[6] Based on adult mortality due to severe cranial injury, the occurrence frequency of BD due to severe cranial injury in children is estimated to be approximately 40%.

Serious cranial injuries in children are often cases of multiple injuries (multiple organ damage), and hypotension and hypoxia accompanying organ hemorrhage markedly exacerbate secondary brain damage. Stewart et al.[19] analyzed 180 cases of serious cranial injury and reported that 113 (63%) had a serious injury in another site. An injury of the chest region occurred at the highest frequency and accounted for 84% of those with multiple injuries. In addition, the factors that were related to mortality included pupillary findings upon presentation, hypotension, and history of blood transfusions. Thus, death seems to be unavoidable in a certain proportion of patients, and it is likely that medical professionals involved in treating pediatric cranial injury cases are highly involved in BD determination.

Pediatric BD: Unresolved Problems

I. Variability and quality of BD determination

Many reports from Western countries have viewed the variability of BD determination as a problem. Mathur et al.[20] analyzed in detail the determination of BD in children aged 18 years and younger in Southern California. They found that the site of BD determination and qualifications of those who performed this determination varied, thereby indicating that BD determination records were insufficient, and there was a tendency to determine BD based on CBF testing alone. Therefore, as a means of countering these problems, they argued the necessity of a unified form of BD determination throughout the United States. Shappell et al.[21] investigated the rate of performing brainstem reflex testing in 226 brain-dead organ donors in 2011 at 68 medical facilities throughout the Midwest region of the United States. They found that of the 102 cases (45.1%) with neurological findings recorded in medical records, oculocephalic reflex, vestibular reflex, and gag reflex were noted in 79.6%, 65.9%, and 68.6% of the cases, respectively. The authors expressed concern regarding the fact that organs are being donated based on an incomplete determination of BD without uniform criteria. Meanwhile, Stockwell et al.[22] prepared a standard format and checklist for determining BD on electronic medical records and reported that BD determination in the PICU became uniform and more concordant with the facility's diagnostic criteria. There were many problems with BD determination, such as missing records of the date and time of BD determination performed, missing records of vital signs, omissions of the oculocephalic reflex and vestibular reflex, and BD determination without taking medications used into account.

The results of a fact-finding survey on the determination of BD in children in Japan are based on responses obtained from 67 of 1,220 (5.5%) facilities surveyed over 11 years and 1 month from April 1987 to April 1999. Of the 139 subjects with BD, both apnea testing and neurological examination were

conducted at least twice on 20 cases (14%), and this number increased to 30 (21%) when cases that underwent apnea testing only once were included. Similar results were indicated by primary and secondary surveys conducted by the Japan Pediatric Society (Working Group for Basic Infrastructure for Organ Donations by Brain-Dead Children) and the Japanese Society of Child Neurology (Conference for Verifying Criteria for Brain Death Determination in Children) from May 1999 through to the beginning of 2004, which found that it was only in 11 of 74 (15%) cases that apnea testing was performed. Mizuguchi[23] has indicated the following reasons for the low rate of apnea testing: (1) there was little practical significance in officially determining BD in children aged under 15 years because they could not donate organs at that time; (2) "general" determination of BD is sufficient for the purposes of grasping the patient's status, determining treatment strategy, and giving an explanation to the patient's guardians; (3) apnea testing is highly invasive and risky; and (4) it can be difficult to obtain informed consent from the patient's guardians.

In the United States, the development of educational programs to unify determination criteria and improve the precision of BD determination is gaining attention. It can at least be considered that there is no variability in legal BD determination in Japan, and a summary of 150 cases[24] with completed verification has been published (Fig. 4).

II. Chronic BD

The MHLW report "Research regarding Determination of Brain Death in Children and Organ Donation" found that chronic BD (long-term BD; it took at least 30 days to reach cardiopulmonary arrest after determination of BD) accounted for 20% of all cases.[11] Baker et al.[25] have hypothesized that developments in intensive care medicine have lengthened the time from BD determination to cardiopulmonary arrest. Currently, respiratory and circulation management is proactively performed even on brain-dead patients, and if care is taken with respect to elements such as prevention of infection and nutritional management, it is generally accepted that a heartbeat can be maintained over a long period. Chronic BD was previously considered to be specific to children, but this was greatly attributable to a report by Shewmon.[26] In this report, he analyzed 56 brain-dead patients who survived for at least a week after diagnosis and concluded that patients who met the clinical criteria for BD have not necessarily lost integrated physical functioning, and many cases do not require intensive care equipment to stabilize their organs other than their brain. Wound healing, improvement from infection, fever, and growth can be observed even in brain-dead patients. Furthermore, integration of the individual is built on a reciprocal relationship between each part of the body, and it does not work in the way that the most important organs forcibly control other organs in a top-down manner. Because some of the reported cases of "BD" included cases that did not strictly meet the determination criteria, the precision of such diagnoses was criticized. Even to date, no conclusion has been reached regarding whether chronic BD should be considered as a pathology peculiar to a child or a result from the influence of intensive care medicine.

In 2008, when the President's Council on Bioethics (PCBE) compiled the white paper "controversies in the determination of death,"[27] cases of chronic BD

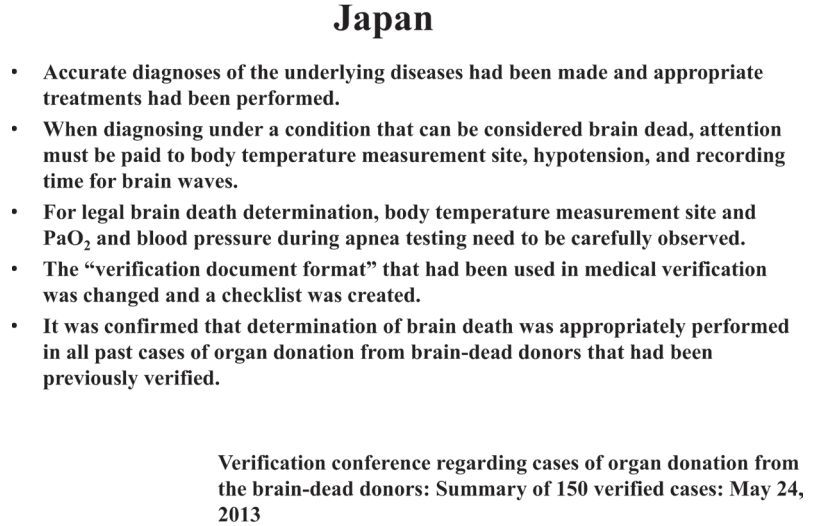

Fig. 4 Summary of 150 cases by verification conference regarding cases of organ donation from the brain-dead donors.

were investigated. Results indicated that there are clear differences between the linguistic representation of the conventional definition of BD and the clinical state of patients diagnosed with BD, which is candidly accepted. Shewmon's evidence required the abandonment of reasoning relying on the premise that the brain conferred integrative unity on the organism as a whole. He showed there was no necessary connection between brain activity and some integrative somatic unity. The white paper admits that if expressions of integrative somatic activity were sufficient to indicate the presence of a whole living organism, then the neurological criteria would have to be abandoned as a standard for ascertaining human organismic death. However, the white paper finally does concede Shewmon's point about the role of the brain in mediating integrative unity and rejects the conclusion that some expressions of somatic integrative unity are expressions of a living whole. Eventually, it was determined that the term "brain death" was inappropriate, and they proposed to change it to complete brain failure. It is highly commendable that the PCBE considered a preconceived idea in its own country to be "unreliable" and redefined it.[27)]

BD in children based on certain criteria is determined in only a few countries around the world,[28)] and it is difficult to perform scientific analysis on pediatric patients. However, the amount of detailed information available regarding the epidemiology and pathology of BD in children has recently increased.[16,29)] In Japan, the perception that the BD diagnosis is performed for the purpose of organ donation remains strong. Furthermore, in many cases, BD is not determined and the family members are given explanations based on the practitioner's subjective view such as "almost brain dead," "a brain-dead state," or "infinitely close to brain dead." Therefore, the "limitations of life-saving" are presented before a diagnosis of BD and intent to donate organs by the family is confirmed at this point. The overuse of the term "BD" not only affects medical care but also legal interpretations and may eventually impede the understanding of the patient's family and influences the trust of doctor–patient relationship.

It is rational to determine what may be the beneficial treatment for the patient based on an understanding of "BD" as the limitation of treatment for the underlying disease. We must not forget that it is the clinician's premise to share sufficient treatment information and increase mutual understanding so that the biased pursuit of efficiency does not destroy the trust of the patient and his/her family, which should be rightfully obtained. Therefore, strict criteria for diagnosing BD must be used, and this is an essential issue for the future of pediatric emergency medicine and intensive care in Japan.

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Conflicts of Interest Disclosure

The authors declare that they have no conflict of interest.

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