Report on the Criteria for the Determination of Brain Death in Children

—1999 Report of the Study Group on the Criteria for Determination of Brain Death in Children, Ministry of Health and Welfare—

Part II: Determination of Brain Death in Children in Japan

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Cerebral Characteristics Related to Brain Death in Children

Brain death is a clinical concept defined as "irreversible loss of whole brain functions," irrespective of age.[1–4] Brain functions, as referred to in this context, are those that can be tested clinically, and brain death is diagnosed in the presence of irreversible deep coma, absence of brain stem reflexes and apnea; their irreversibility can be determined clinically in children as well as in adults.

However, it is believed that, in children, particularly in infants, the brain is resistant to various stresses, including hypoxia,[1,5,6] and recovery of function may occur even after prolonged loss of certain brain functions. Although there is poor scientific evidence to definitively corroborate such clinical experience, the possibility nevertheless indicates the necessity for prudence while determining the irreversibility of brain functions in children.

Some characteristics important to the understanding of brain death in children are discussed in this section.

(1) Resistance to stress

Resistance of the brain in children, particularly infants, to certain stresses has not yet been fully ascertained. However, compensatory reactions and resistance to hypoxia and/or edema at the cellular level and their pathophysiological significance in the progression of brain damage in infants have been reported, and may represent characteristic features not noted in adults.[7–11]

(2) Anatomical aspect

The brain and cranium of a child have several anatomical characteristics, which may influence the pathological progression of brain

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death. Among them, the distensibility of the cranial cavity by virtue of the easy dissociation of the cranial sutures is important. The unique blood supply to the brain and meninges through both the carotid and vertebral arteries also serves to prevent the progression of brain damage.[12] On the other hand, cerebral blood vessels in children are known to be very fragile, and even slight changes in blood pressure or flow can easily cause intracranial hemorrhage.[13]

(3) Neurological aspect

As is evident from the rapid growth of the head circumference of a neonate after birth, the brain at the infantile stage undergoes rapid growth and development. The function of the central nervous system varies according to the days, months or years after birth.[14–16] This is also accompanied by the development of various reflexes and appearance of waves in the electroencephalogram (EEG). Therefore, specific knowledge and experience of these tests are necessary for accurate evaluation during the phase of growth.

In adults, neurological diagnosis of brain death is straightforward, except in complicated cases. However, in small children, age-related development of the brainstem reflexes and the EEG pattern must be considered and the various neurological and adjunctive tests required, in particular, invasive tests, are difficult to perform due to the limitations posed by the body size.[17]

(4) Cause of brain death

There is a significant difference in the etiological pattern of brain death between children and adults. According to a survey, mainly of adult cases, conducted by the Brain Death Study Group of the Ministry of Health and Welfare (MHW) in 1985,[18] primary brain damage was more frequent than secondary brain damage, such as hypoxic brain damage, with a primary to secondary brain damage ratio of 92:8. In contrast, our present survey revealed a primary to secondary brain damage ratio of 57:43. Brain death due to cerebrovascular disease, a primary cause of brain damage common in adults, particularly in those of middle to advanced age, is not frequent in infants,[19–21] while the frequency of secondary damage is high in infants.

As is typically represented by intracranial hemorrhage, most cases of primary brain damage follow a rapid and definite clinical course. In contrast, most cases of secondary brain damage follow a variety of clinical courses, while not necessarily progressing rapidly.

(5) Time between brain death diagnosis and the occurrence of cardiac arrest

The duration between the diagnosis of brain death and the development of cardiac arrest tends to be markedly longer in children than in adults. The same trend had already been pointed out by the Brain Death Study Group of the MHW in 1985.[1] This may be in accordance with the reported results that the more active the management of the patient is, the stronger this trend is.[19,22] However, the time difference of more than 10 years between the two surveys, and the influence of advances in emergency and intensive care on the results must be considered, and it may not be entirely reasonable to conclude that this trend is characteristic of only children.

Criteria for the Diagnosis of Brain Death in Different Countries

The criteria for the diagnosis of brain death in children in different countries, published in scientific journals, governmental publications (including those collected through overseas agencies of the Ministry of Foreign Affairs), or in major articles published by researchers from the respective countries, are cited. However, it is possible that there are some other criteria in addition to those cited below in each country.

(1) Australasia

1) Australia and New Zealand

According to the "Recommendations Concerning Brain Death and Organ Donation" published in 1993 and revised in 1998 by the Working Party of the Australian and New Zealand Intensive Care Society,[23] the criteria for the diagnosis of brain death in adults are also applicable to children aged 2 months or older. For infants aged less than 2 months old, an observation period different from that in older children and adults is recommended, but no specific length of time has been specified.

2) Korea

"Law Concerning Transplantation of Organs" was officially announced in 1999 and enforced in 2000. According to this law, for the diagnosis of brain death in children under 6 years of age, the criteria for brain death in children aged 6 years or older must be satisfied. Moreover, confirmatory tests, including EEG, should be performed at 48 h in infants aged between 2 months and 1 year, and at 24 h in children aged between 1 year and 6 years. In children aged 6 years or older, confirmatory tests should be conducted after 6 hrs (according to investigation by the MHW).[24]

(2) North America

1) Canada

Although the Canadian Medical Association proposed guidelines for the diagnosis of brain death in 1987 with the approval of the Canadian Neurological Society,[25] it remained unresolved as to whether or not the criteria applicable to adults could also be applied to neonates and infants. However, brain death was diagnosed at the Hospital for Sick Children in Toronto according to the hospital's own criteria for the diagnosis of brain death, laid down based on the aforementioned guidelines.[26] Later (1998), new guidelines were developed by the Canadian Neuro-Critical Care Group, including the Canadian Neurological Society. According to these guidelines, the criteria for the diagnosis of brain death in adults can be applied to children aged 2 months or older. However, for the diagnosis of brain death in infants between 7 days and 2 months old after full-term birth, RI examination of the cerebral circulation in addition to clinical examination is required. For children between 2 months and 1 year of age, repeat EEG after an interval of 24 h or longer is desirable. However, if the cerebral arteries cannot be visualized by RI cerebral angiography, there is no need to repeat the EEG. Observation for at least 12 h is recommended in the case of children over 1 year of age, and for at least 24 h in cases of cerebral hypoxia. These criteria are not applicable to infants born before full term (before completion of 38 weeks of gestation) and neonates under 7 days old, even if they were born at full term.

2) U.S.A

Although the US Presidential Committee published criteria for the diagnosis of brain death in 1981, children under 6 years of age were excluded from these criteria. Later, in 1983, Rowland *et al.*[7] stated, based on their experience with 15 children who were in coma and had apnea and absent brainstem reflexes, that brain death in children can be diagnosed according to the criteria applicable to adults after 3 or more days of observation. Of their 15 cases, liquefaction and necrosis of the brain were confirmed in 11. Then, Walker (1985)[28] pointed out the difficulty of diagnosing brain death in children under 5 years of age, and recommended repeat confirmation of a flat EEG recorded for 30 min at 24 h in addition to neurological testing, followed by final confirmation with an apnea test. A similar procedure was also advocated by Suter (1993),[16] who used a repeat EEG plus cerebral angiography, RI scan, or evoked potential examination at 24 h in cases of doubt. Moshé *et al.* (1988)[29] reported that the criteria for the diagnosis or brain death involving EEG and brainstem auditory evoked potential testing may be appli-

cable to children aged under 5 years old. However, they also emphasized that this should be confirmed by a nationwide multi-center cooperative study covering a large number of cases. In a study which examined brain death in 61 children who were all younger than 6 years old (including 51 infants), the usefulness of EEG and the RI angiography 48–72 h after the diagnosis of clinical brain death was noted.[20)]

In 1987, the US Task Force for the Determination of Brain Death in Children (constituted by 10 representatives from related medical societies, legal associates, National Institute of Health, etc.) published "Guidelines for the determination of brain death in children." These guidelines are similar to the criteria proposed by the US Presidential Committee, except that the observation period was longer according to whether the subject is a neonate, infant, or older child, and according to the cause of brain damage. These criteria could be applied to all infants born after 38 weeks of gestation (full term birth), when 7 or more days had elapsed after the occurrence of brain damage. Among the adjunctive tests, EEG and RI angiography were suggested for reducing the time period required for the confirmation of brain death.

These guidelines were accepted favorably by related societies, but Shewmon pointed out the risk of false-positive diagnosis (non-brain death cases diagnosed as brain death).[30,31)] In response to this argument, the Task Force explained that the guidelines were developed based on experience with its own cases and on the available data on adult cases, since published information on children was insufficient. The Task Force contends that these guidelines are not final, and are subject to further revision after the accumulation of relevant data, although there has been no known case of successful resuscitation after diagnosis of brain death had been made according to these criteria. Kohrman *et al.*[32)] and Okamoto *et al.*[33)] also call attention to the risk of false-positive diagnosis, reporting that in some cases who fulfilled the criteria of the Task Force, the cerebral cortical and brain stem functions recovered partially. On the other hand, Fishman stated in a critical review published in the *Pediatrics* that these reports would not affect the reliability of the guidelines.[34)] The reported cases do not fulfill the criteria for the diagnosis of brain death proposed by the present Study Group for various reasons, including non-establishment of the causative disease.

Alvarez *et al.* (1988)[4)] reported that the criteria for adult cases are applicable to children older than 3 months of age, and that confirmation of brain death by a demonstration, once, of a flat EEG is sufficient. Shewmon and other researchers put forward a counterargument.[30,31)]

Ashwal *et al.* (1988),[35)] who carried out a retrospective study of brain death diagnosed in 18 neonates, stated that even clinical evaluation alone would enable a definitive diagnosis of brain death if the judgment is repeated after an interval of 2 days in the case of full-term infants, and 3 days in the case of prematurely born infants. Ashwal *et al.* (1991)[19)] concluded that the guidelines proposed by the Task Force gained general consensus as the valid diagnostic criteria for brain death. According to an extensive survey by Mejia *et al.* (1995),[36)] the guidelines are not strictly implemented nationwide. They pointed out that failure to follow the standard procedure of an apnea test, in particular, is not rare, and urged performance of the apnea test as the most important procedure in the determination of brain death.

(3) Europe

1) Italy

Mazzarella *et al.* (1994)[37)] recommend that in the determination of brain death in children, EEG and the cerebral circulation test must be repeated after an interval of 48 or 72 h for confirmation of brain death.

2) UK

In the UK, the criteria for the diagnosis of brain death were revised in 1995. According to

the report of the British Pediatric Association published in 1991, the criteria for the diagnosis of brain death in adults may be applicable to at least infants more than 2 months old.[38,39] Pallis *et al.* (1996)[40] excluded neonates under the age of 7 days, and advised that caution should be exercised in the diagnosis of brain death in children aged 5 years old or younger.

3) Germany

The German Medical Association Criteria for the diagnosis of brain death, revised in 1991, propose prolongation of the period of observation for confirming the diagnosis of brain death in infants. More specifically, in the case of primary brain damage, an observation period of 72 h is recommended for the diagnosis of brain death in neonates and infants, and 24 h for that in infants under 3 years of age. The observation period recommended for children aged 3 years or older and adults is 12 h.[41,42]

In summary, the criteria for the diagnosis of brain death in various countries indicate that the basic concept of the diagnosis of brain death in children is the same as that in adults, and that the diagnosis is based on neurological tests and adjuvant tests, including EEG and the cerebral circulation test. However, the lower age limit for which these criteria may be applicable ranges widely from 7 days to 2–3 months of life. In general, tests for the determination of brain death are repeated after longer intervals in children than in adults. Although it varies according to the age and the cause of brain damage, the interval for repeat tests, overall, is 24–48 h.

Prerequisites

In Japan, the criteria proposed by the Brain Death Study Group of the MHW in 1985 have been widely accepted as the criteria for the diagnosis of brain death in children aged 6 years or older, and during the last decade, brain death has been successfully diagnosed according to these criteria. In developing criteria for the diagnosis of brain death in children under 6 years of age, we believe that the diagnosis should be made basically in accordance with the criteria proposed by the Study Group of the MHW, because the concept of brain death is consistent, regardless of age.[3] Namely, brain death can be diagnosed in children, as in adults, by the presence of deep coma, absence of brainstem reflexes, presence of apnea as determined by a rigorous apnea test, and electrocerebral silence (ECS). Since there is no fundamental difference in the concept of brain death among different countries, and the aforementioned criteria from overseas are also expected to be very helpful in developing the criteria in Japan.

The 1984 survey by the Brain Death Study Group of the MHW reported 26 cases of brain death in children under 6 years of age. The present survey managed accumulation of 139 cases. Based on the present data and the relevant literature, the criteria for the diagnosis of brain death in children under 6 years of age are proposed as follows.

1. Subjects

As in adults, the patients in whom determination of brain death is indicated are; those in apneic deep coma with organic brain damage, maintained on artificial ventilation, in whom the cause of brain damage has been diagnosed definitively, and in whom there appears to be no hope of recovery even after appropriate application of all the currently available therapeutic interventions. Demonstration of the cause of the pathologic process by CT and other radiographic examination modalities constitutes an essential part of the diagnosis of brain death in children, as in adults.

2. Exclusion

(1) Age

As reviewed in the section of neurological characteristics, in children under 12 weeks old, the EEG shows slow-wave activity, and brainstem auditory evoked potentials are variable during this stage; therefore, electrophysiological diagnosis of brain functions may be difficult in children at this stage of life.

In Australia, New Zealand and UK, the criteria applicable for the diagnosis of brain death in adults are applied only to children aged 2 months or older. For infants under 2 months old, Canadian 1999 guidelines mandate the performance of the RI cerebral circulation test in addition to clinical tests; furthermore, the guidelines followed in Australia/New Zealand guidelines also mandate prolonged observation.

More importantly, the present survey included only 9 cases of infants under 12 weeks old. Therefore, we excluded infants less than 12 weeks of adjusted age (calculated from the estimated birth date) from the purview of these guidelines.

(2) Hypothermia

Since hypothermia affects brain functions, it is desirable that the body temperature is near normal at the time of determination of brain death. Consciousness may be disturbed below 35°C, and lethargy and disorientation are often observed at a body temperature of 35–32°C.[43] In addition, as the body temperature decreases, the slow-wave component in the EEG becomes predominant;[44] at 30°C or less, however, it is suppressed, and at 20°C or less, the EEG becomes flat.[45]

In the present survey, the body temperature was maintained above 35°C in more than 80% of the cases. Hypothermia is unequivocally excluded from the purview of the guidelines for the diagnosis of brain death in different countries, and we also consider that cases with hypothermia less than 35°C should be excluded.

(3) Drug effects

Central nervous system depressants, anticonvulsants, muscle relaxants and some other drugs could potentially affect the diagnosis of brain death. If drugs having central nervous system depressant activity have been used, it is desirable to determine brain death after the blood concentration of the drug has decreased to below the effective dose. For example, the half-life of phenobarbital is 37–55 hs in infants.[14,15]

It has been reported that there are no effects on the outcome if the administration of barbiturates is discontinued at the time of determination of brain death, and if other criteria of brain death are satisfied at or under the therapeutic blood concentration of the drug (15–30μg or 20–40μg).[46] In addition, the half-lives of phenytoin and diazepam in young children (infants) are reported to be 11–31 (39–55) and 14–20 (8–12) h, respectively.[14,15]

In recent years, short-acting thiopental, midazolam and lidocaine have been used in some cases of status epilepticus associated with acute encephalopathy or encephalitis. These drugs generally have short half-lives, and the consciousness-suppressant activity of phenytoin and lidocaine is low.[47,48]

If muscle relaxants have been used, the time of administration should be taken into consideration, and the absence of residual drug effect should be confirmed with a nerve stimulator if necessary. When central nervous system depressants have been used, the blood concentration should be determined if possible, and the drug effect should be judged comprehensively, taking into account the half-life of the drug and other factors.

(4) Metabolic, endocrine disease and other conditions

It is appropriate to exclude cases of metabolic disorders or endocrine disease (glycogen storage disease, congenital disorders of organic acid metabolism, congenital adrenal hyperplasia) which are associated with acute hypo-

glycemia or serious acidosis from the purview of these guidelines, because contribution of these diseases to deep coma are currently uncertain, even if the diagnosis of the disease itself is clear.

Although the guidelines proposed by the Task Force exclude surgically curable situations,[6,36] it is needless to say that determination of brain death should be done in all patients showing no possibility of recovery of brain functions even after application of all currently available therapeutic interventions. In the UK, pediatric cases of brainstem death due to acute poisoning and metabolic disorders are excluded.[40] In Canada, the criteria for the diagnosis of brain death in adults exclude from their purview cases with brain damage of unknown etiology, trauma that precludes ophthalmologic examination unilaterally or bilaterally, middle ear injury, cranial neuropathy, and severe lung disease. These exclusion criteria are also applicable to pediatric cases. Exclusion of patients with brain damage of unknown etiology is widely accepted in many countries.

In other patients in whom complete evaluation of neurological testing is impossible, confirmatory tests such as cerebral blood flow test can be used.[25] In Germany[41] and Korea, adult criteria are also applied to pediatric cases, and therefore cases of metabolic disorders and endocrine diseases are excluded. Diagnosis of brain death, however, can also be confirmed by demonstrating the cessation of cerebral blood flow, as in Canada.

If eye injury, middle ear injury, or high spinal cord injury partially preclude brain stem reflex testing or apnea testing, adjunctive tests such as brainstem auditory evoked potential and cerebral circulation tests may facilitate a comprehensive determination of brain death. However, such cases should be excluded just as in the case of adults, until the current law in Japan remained unrevised.

Basic Considerations

Diagnosis of neurological symptoms in children is difficult as compared to that in adults. Therefore, diagnosis of brain death in the pediatric age group must be performed by physicians who are skilled at neurological examination and intensive care of children. Meticulous evaluation is mandatory before pronouncing brain death.

1. Vital Signs

The level of consciousness is discussed in Section 2; Neurological symptoms. The body temperature is an important parameter in the diagnosis of brain death.

Confirmation of irreversible loss of respiration is an indispensable element in the determination of brain death. Therefore, the apnea test is necessary to confirm the absence of spontaneous respiration in the patient, and will be discussed in detail in Section 4; Respiration.

(1) Body temperature

As previously described, neurological findings are modified by hypothermia, which is excluded from any criteria for the diagnosis of brain death. Since body temperature is artificially controlled in the intensive care setting, it is, in general, not difficult to maintain body temperature above 35°C within the range of near normal body temperature.

Axillary temperature is about 1°C lower than the core body temperature, because of the vasoconstriction of cutaneous blood vessels and evaporation from the skin. Therefore, measurement of the core temperature (rectal, esophageal, vascular [via Swan-Ganz catheter]) is recommended.

(2) Blood pressure

Brain death may cause an abrupt fall of blood pressure. Such hypotension usually follows the arrest of spontaneous respiration.

Table Brain Stem Reflexes for the Determination of Brain Death in Children

Reflex / Institutes	Light reflex	Corneal reflex	Oculocephalic reflex	Ciliospinal reflex	Vestibular reflex	Pharyngeal reflex	Cough reflex	Suckling reflex	Rooting reflex	Aschner reflex	Same as adults
Task Force (TF)	○	○	○		○	○	○	○	○		
MGH	○	○			○						○
Children's Hospital, Boston	○	○	○		○	○	○	○	○		
Children's Hospital, Los Angels	○	○	○		○	○	○	○	○		
Children's National Medical Center, Washington DC	○	○			○						
Children's Hospital, Atlanta	○	○	○		○	○	○				
Loma Linda University	○	○	○		○						○
Suter (1984)	○		○		○						
UCSF (1986)	○	○	○		○	○	○				○
Drake (1986)	○	○	○		○	○					
Solomon (1986)	○	○	○		○	○				○	○
Ashwal (1989)	○	○	○		○	○		○			
Hospital for Sick Children, Toronto	○	○	○		○	○	○				
Barker (1998)	○	○			○		○				○
Pallis (1996)	○	○	○		○	○	○				○
ANZICS (1998)	○	○	○		○	○	○				○
German Medical Association (1991)	○	○	○				○				○
Sweden (1987)	○	○	○				○			○	
Present criteria proposed by the MHW Study Group	○	○	○	○	○	○	○				○

TF: Task Force for Determination of Brain Death in Children (U.S.A.)
MGH: Massachusetts General Hospital
UCSF: University of California, San Francisco/Stanford University
ANZICS: Australia & New Zealand Intensive Care Society
MHW: Ministry of Health and Welfare (Japan)

However, patients with possible brain death are often on cardiovascular stimulant drugs, and therefore, hypotension is not a valid ground for the determination of brain death.

It is possible that cerebral hypoxia resulting from hypotension modifies the level of consciousness and neurological findings. It would be desirable to perform neurological examination while the blood pressure is maintained at as normal value as possible.

(3) Heart rate

Like blood pressure, the heart rate is controlled by central and peripheral mechanisms.

In addition, the automaticity of the heart must also be considered. Therefore, it is not appropriate to consider variation of the heart rate itself as a ground for the determination of brain death. Patients with severe arrhythmias may not endure the apnea test, and should be excluded if any circulatory insufficiency is anticipated.

2. Neurological Symptoms

(1) Level of consciousness

There must be deep coma with complete absence of any voluntary movements. For evaluation of the level of consciousness in children, Sakamoto's 3-3-9 method[49] (a modification of the Japan Coma Scale for children) and a pediatric version of Glasgow Coma Scale are available. These evaluation procedures consider the same criteria as those in adults for the diagnosis of deep coma, although the criteria for mild to moderate disturbance of consciousness are different from those in adults.

(2) Pupils

It is necessary to confirm before the diagnosis of brain death that the light reflex is completely absent, and that the pupils are fixed and dilated bilaterally. There may be age-related differences in the eye size and pupillary diameter in healthy children. In the present survey, however, the pupillary diameter was 4 mm or more in all cases of group I + II, with an average of 5.0–5.9 mm. Therefore, dilatation of the pupils to a diameter of 4 mm or more is basically used as a criterion in the determination of brain death.

(3) Brainstem reflexes

In the present survey, absence of brainstem reflexes was confirmed in all patients of group I + II, just as in adult cases, except in 3 patients in whom the results of the vestibular reflex test was unclear. On the other hand, in group III + IV, the frequency of testing of the vestibular reflex, oculocephalic reflex, and ciliospinal reflex was low.

The table shows the brainstem reflexes tested for the determination of brain death in pediatric cases in various countries. Those included in the draft guidelines proposed by us were consistent with the criteria employed in various other countries. Although it still remains controversial as to which of the brainstem reflexes should be examined in pediatric cases, there are no remarkable differences among the criteria employed in various countries and among the reports by researchers.

Response to sound, light reflex, corneal reflex, oculocephalic reflex, Moro's reflex, and the grasp reflex are already well developed in fetuses by 30–36 weeks of gestation.[19] Therefore, except in infants under 12 weeks of age (adjusted age), there is no need for considering developmental factors in the testing of brainstem reflexes.

For this reason, we believe that, just as in adult cases, the light reflex, corneal reflex, ciliospinal reflex, oculocephalic reflex, vestibular reflex, pharyngeal reflex, and cough reflex are indispensable for the diagnosis of brain death in infants aged 12 weeks or older, the subjects covered in the present survey.

* Although there are no particular differences in the procedures employed for the testing of brainstem reflexes, it must be noted that consideration should be given to the volume of ice water irrigated into the auditory canal for the caloric reflex; while a volume of 50 m*l* is used in adults, it should be reduced to as low as 10 m*l* in some pediatric cases. It is important to allow the ice water to overflow from the external auditory canal, and to keep the canal at a constant temperature.

(4) Spinal reflex

In the present survey, some spinal reflex was positive in 8 of 20 cases in group I + II, and 12 of 53 cases in group III + IV. While the incidence of positive spinal reflex in adult cases of brain death has been reported to be about 7%

(the Brain Death Study Group of the MHW),[18] the incidence in children with prolonged brain death in the present survey was even higher. However, the brain was already lysed or liquefied in autopsied cases. In most cases with a positive spinal reflex, diffuse low density areas were confirmed by brain CT even when autopsy was not performed. Thus, these results indicate that the presence of the spinal reflex does not interfere with the diagnosis of brain death in the pediatric age group.

Motor reaction stimulated by filling of the bladder, or variations of the blood pressure or heart rate as a manifestation of autonomic nervous reflexes are known to occur in some adult cases of brain death.[50]

3. Electroencephalography (EEG)

(1) Significance of EEG in brain death

For adult cases, a flat EEG has been cited as one of the criteria for the diagnosis of brain death (Rules of Implementation of the Law Concerning Organ Transplant, Ordinance by the MHW, No. 78, in 1997). Flat EEG is defined as the absence of brain-derived waves exceeding the internal noise of the EEG apparatus (electrocerebral silence, ECS), as determined using appropriate techniques. In the pediatric intensive care unit, the EEG pattern is confounded by many artifacts, on account of the number of life support systems and the complicated flow of personnel. Therefore, elimination of the influences of the electric and mechanical noises generated by various sources is an important issue.[51]

While the diagnostic value of EEG, which represents the electrical activity mainly of the cerebral hemisphere, is high, EEG data alone are insufficient for evaluating the whole brain functions. Analysis of EEG and simultaneously recorded brainstem auditory evoked potentials has shown that the loss of cerebral functions and brainstem functions do not necessarily coincide with each other temporally.[52,53] The same findings were also noted in pediatric cases.[54]

However, EEG is the most widely used and well-known technique among the adjunctive tests performed for the diagnosis of brain death in pediatric cases.[14,15,19] This was also noted in the present survey. As long as the concept of cessation of whole brain functions is adopted, the EEG would remain an important test, and EEG is strongly recommended for the diagnosis of brain death in infants, particularly in neonates, in whom neurological findings are difficult to evaluate.[6,14,15,41,55,56]

(2) EEG characteristics in children

It is well known that the EEG pattern changes each month or year as children grow. Developmental changes in the EEG are more conspicuous in younger children. For instance, the background activity in premature infants takes on a nearly flat pattern with extremely low amplitude. The electrical potential is also generally low in neonates born at full term. When there is some brain damage, the low potential is more conspicuous and more prolonged. In normal infants, the low potential is no longer noted after 2 or 3 months of life, and regular and obvious waveforms, which may be called sleep spindles or humps, are noted.[57] In addition, neonates spend most of their time sleeping, and show differing EEG patterns according to the depth and phase of sleep. In the REM sleep phase, which is characterized by rapid eye movements, the EEG shows a low electric potential. With the passage of time after birth, the REM sleep phase becomes shorter, but still accounts for 50% of the sleep phases in children at 1 month of age.[58–60] Therefore, due caution must be exercised while evaluating low-potential EEG in infants who are only a few months old.

Nonetheless, it is reasonable to assume that a flat EEG is indicative of brain death in infants over 12 weeks old (adjusted age), excluding cases of drug intoxication and hypothermia.

(3) Method of EEG recording

The report by the Brain Death Study Group of the MHW has described the method of EEG recording. However, because of current advances in the technique and improvements in the equipment, and also discordance in the application to children, we define the method as follows.

It is necessary to eliminate noises generated by various sources in cases where EEG recordings are conducted as a part with the purpose of determination of brain death.

(i) Lead

Electrodes should be placed at Fp1, Fp2, C3, C4, O1, O2, T3, T4 and Cz (10-20 International Method), to cover a wide area of the cerebrum, with the reference electrodes placed on the right and left ear lobules. Since ECG artifacts can arise from the ear lobule, the reference electrodes may be placed at a site just anterior to the papillary tubercle, or at the upper margin of the ear lobule.

Electrodes should be placed at intervals of at least 7 cm. Reference electrode leads (6 leads) using these electrodes and the reference electrodes at the ear lobules, and bipolar leads (4–6 leads), with connections among the electrodes, should be employed.

While the location of the electrode may be modified in the case of injury, surgical wound, or cranial deformation, such modifications should be recorded.

(ii) Time of examination

EEG data should be recorded for at least 30 min.

(iii) Sensitivity of the EEG equipment

EEG data should usually be recorded at 10μV/mm, but a part of the recording should be made at a higher sensitivity, e.g., 2μV/mm.

(iv) Time constant and high-pass filter

A time constant of 0.3 sec and a high-pass filter of 30-Hz or higher should be used.

(v) Electrode placement impedance

The placement impedance of each electrode should be kept 5 kΩ or less.

(vi) Concomitant recording

To detect artifacts, ECG monitoring should be carried out. The ECG electrodes should be placed on the upper arm, forearm, or back of the hand.

(vii) Setting of the recording speed

Recordings should be obtained at a speed of 30 mm/sec. Data may be stored as digital data.

(viii) Stimulation during EEG recording (Caution is necessary to ensure that the action providing the stimulus does not affect the recording or elicit the spinal reflex.)

· Calling the name: Call out the patient's name or make a loud sound near his or her ears.

· Pain stimulus to the patient's face.

4. Respiration—Apnea Test

Irreversible cessation of spontaneous respiration is an important criterion for the diagnosis of brain death in children, as in adults. The rationale and procedures of the apnea test in children are the same as those in adults.[61] Artificial ventilation is discontinued after ensuring that the patient is not at risk for hypoxemia, and the absence of spontaneous respiration is confirmed by a $PaCO_2$ challenge. The apnea test should be carried out after the neurological and EEG examinations have been performed.

(1) Stimulation of the respiratory center by CO_2

Regardless of whether the patient is an adult or a child, it remains controversial as to how high the $PaCO_2$ level should be to stimulate the chemical receptors of the respiratory center in patients with brainstem lesions, in the presence of a high PaO_2. It is widely accepted that the same level is applicable to adults and children,[62] and it is considered that a $PaCO_2$ level of 60 mmHg or higher is probably appropriate.

In all cases examined by the apnea test in the present survey, the results were positive (apnea). In these cases, the $PaCO_2$ level was

sufficiently high, touching 80 mmHg, on average. Although the US Task Force guidelines do not specify the $PaCO_2$ level or duration of discontinuation of artificial ventilation, related articles have been cited. More specifically, a report documenting that no spontaneous respiration occurred at a $PaCO_2$ of 55–112 mmHg (median, 74 mmHg) in 60 children that were 5 years old or older (retrospective study),[63] and another documenting that no spontaneous respiration occurred at a $PaCO_2$ of 54–91 mmHg in 24 children that were 10 years old or younger (prospective study),[64] are cited.

It has been reported that in a case of severe asphyxia at birth at 37 weeks of gestation that fulfilled the Canadian criteria of brain death, spontaneous respiration occurred at a $PaCO_2$ of 59 mmHg.[65] Sixteen sessions of apnea testing in 9 children aged between 4 months to 13 years of age revealed the absence of spontaneous respiration at a $PaCO_2$ of 50–116 mmHg.[9] It has also been reported that no spontaneous respiration occurred in 10 children aged between 10 months and 13 years of age when artificial ventilation was discontinued for 5 min during which time the mean $PaCO_2$ increased to 59.5 mmHg.

Some researchers suggest that discontinuation of artificial ventilation for 5 minutes is sufficient for children, because elevation of the $PaCO_2$ to 60 mmHg is considered to be sufficient, and because the higher basal metabolism in children allows for a more rapid increase of the $PaCO_2$.[14,15,62]

However, there is the view that a $PaCO_2$ level of 60 mmHg may be insufficient in some pathological conditions.[10] Vardis *et al.* recommend an increase of $PaCO_2$ to 100 mmHg or higher in cases of posterior cranial fossa lesions.

Thus, the target level of $PaCO_2$ is, in general, considered to be 60 mmHg or higher. In specific cases, the respiratory center may remain responsive even after the functions of most parts of the brain have ceased. Therefore, further accumulation of data is necessary for cases with such lesions.

(2) Cautions for the apnea test

(i) Preparation before the start of the test

The apnea test should be carried out by a physician skilled in the respiratory management of children, while monitoring the heart rate, blood pressure, ECG, oxygen saturation (SpO_2) by pulse oximetry, and periodic arterial blood gas analysis. Even when it is apparent that the subject does not meet the exclusion criteria for brain death determination at the time of the apnea test, the absence of residual effects of sedative drugs and muscle relaxants should be reevaluated.

The core temperature (esophageal, rectal, or vascular temperature) should be 35°C or higher, and a PaO_2 level of 200 mmHg or higher is desirable before the start of the test. It should be ascertained that the $PaCO_2$ level ranges between 35–45 mmHg.

(ii) Test procedure

After denitrogenation by artificial ventilation with 100% oxygen for at least 10 min, artificial ventilation should be discontinued and replaced by oxygenation with 100% oxygen (6 *l*/min) via a T-piece (Jackson-Rees system). The patient should be observed for respiratory movements during the discontinuation of ventilation. The use of an auto-inflatable resuscitator (so-called Ambu bag) should be avoided because it provides greater resistance to spontaneous respiration and a smaller oxygen reservoir volume as compared with the T-piece. Oxygen insufflation via a catheter inserted in the tracheal tube is not advocated because the size of the tracheal tube is small, and it may be difficult to identify a catheter of adequate size to allow adequate oxygen flow in children of various age groups. In particular, if a large volume of oxygen is allowed to flow through a large catheter wedged in the trachea, overinflation of the lung may cause pneumothorax and circulatory depression.

In patients who need a high mean airway

pressure for the maintenance of oxygenation, it is necessary to perform the apnea test while keeping the patient connected to the ventilator. When the patient is kept connected to the ventilator, the possibility that the patient's heart beats or leakage of air from around the tracheal tube may trigger mechanical ventilation must be borne in mind.

(iii) Judgment of results

The presence of spontaneous respiration should be determined by visual observation and chest auscultation. It should be noted that contact with the stethoscope may induce the spinal reflex.

With regard to the rapidity of increase in the $PaCO_2$ during the apnea test, the increase has been reported to occur at the rate of about 5 mmHg/min during the first 5 min, and about 3 mmHg/min during the subsequent 5 min, when the aforementioned T-piece method is used.[66] However, this cannot be predicted accurately. As long as there are no changes in the blood pressure, heart rate or SpO_2, sampling of arterial blood 5 min after the start of the test to predict the necessary pattern of increase is practical.

Observation should be complete when the $PaCO_2$ reaches 60 mmHg or higher, and the test should be judged as positive (absence of spontaneous respiration) if no respiratory movements are observed at that time.

(iv) Discontinuation of the test

SpO_2 should be maintained at higher than 90% throughout the duration of the apnea test, and if the patient's condition deteriorates, as evidenced by hypotension and/or severe arrhythmia, the test should be aborted immediately, and artificial ventilation with 100% oxygen initiated. Some guidelines recommend the performance of blood gas analysis immediately in the event of a 10% or greater change in the heart rate or blood pressure.[55,67,68]

5. Interval Observation Period

It is common to repeat the determination procedure for brain death after a recommended observation period. However, there is no consensus as to the optimum observation period for repeating the procedures in adults; the same holds true for pediatric cases as well.

As stated in the section "Criteria in different countries" in this document, the time interval varies among guidelines and according to the age of the subject, although on average, it is 24–48 h. Also, it is accepted that a longer interval should be set for pediatric cases; this is because of the general recognition that the frequency of recovery of brain function is higher in children than in adults, based mainly on the experience of experts. This finding is widely accepted worldwide, including in Japan.

In all cases included in the present survey, the interval between the determination procedures far exceeded 6 h, the standard for children aged 6 years or older prescribed by the MHW. In addition, in relation to age, the interval tended to be longer in infants than in young children. The interval also tended to be longer in cases of secondary brain damage than in those of primary brain damage. Although prospective studies in which a provisional determination interval was set showed a tendency towards shorter intervals than in retrospective studies, the interval was still longer than the provisional standard in many cases. This may be a reflection of the very prudent attitude that is usually exercised in the determination of brain death in Japan, especially in pediatric cases.

However, an unnecessarily long interval is meaningless, judging from the fact that all the children in the present survey who were diagnosed as being brain-dead eventually developed cardiac arrest, regardless of the length of the interval to reassessment. In fact, there was no case showing recovery of brain functions between the first determination procedure and the occurrence of cardiac arrest.

The present survey revealed a range of intervals used between the determination procedures, suggesting that the physician-in-charge usually decides the time interval according to individual situations. However, evidently, physicians do not think that longer intervals are associated with higher reliability, because despite the wide range of intervals, the peak intervals were 12 h or 24 h, and the interval, in general, tended be shorter than the provisional standard set in prospective studies.

Thus, the interval between procedures performed to determine and confirm brain death should be set to a value acceptable to the doctors-in-charge in clinical settings, taking into consideration the actual situation in Japan and the practice in other countries. From this viewpoint, the provisional standards, i.e., 48 h for neonates and 24 h for infants, seem to be valid; however, 12 h for young children would seem to be too short, and may be changed to 24 h.

6. "Long-term" Brain Death

In the present survey, long-term brain death (cases in which 30 days or more elapsed between the establishment of brain death and the development of cardiac arrest) accounted for nearly 20% of all cases. In particular, such cases have been significantly more frequent in recent years (prospective studies). This probably suggests the influences of advances in intensive care on the time until the development of cardiac arrest, an issue which was addressed by Barker *et al.*[56] and Cranford.[69]

In a group of brain-dead children who developed cardiac arrest less than 30 days after the diagnosis of brain death, secondary brain damage accounted for about 42% of the cases (38/91), comprising 16 cases of suffocation, 13 cases of drowning, 6 cases of cardiopulmonary arrest, and 3 cases of hypoxia. In contrast, in a group of children with long-term brain death, secondary brain damage accounted for 60% of the children (15/25), comprising 6 cases of hypoxia, 5 cases of suffocation, and 4 cases of drowning. Thus, secondary brain damage tended to be more frequent in the long-term brain death group, but the difference between the two groups was not significant.

There were two cases of very long-term brain death in which cardiac arrest occurred as long as 300 days after the diagnosis of brain death. However, no signs inconsistent with brain death were present during the long course, and diagnostic imaging or autopsy demonstrated liquefaction and/or necrosis of brain tissue.[70,71] These findings indicate that the essence of brain death is irreversible loss of brain functions, and suggest that the time between the determination of brain death and the development of cardiac arrest or the incidence of long-term brain death, is strongly affected by the general management of the patient rather than the cause of brain death.

7. Adjunctive Tests

(1) Evoked potentials

1) Brain stem auditory evoked potentials (BAEP)

If evoked potentials are recorded by a lead from the vertex (Cz) to the ipsilateral or contralateral ear lobule or skin of the mastoid process after a click is given, five positive waves from each point pass through the brainstem. Wave I is considered to be derived from the auditory nerve, wave II from the auditory nerve nucleus, wave III from the olivary nucleus, wave IV from the lateral lemniscus, and wave V from the inferior colliculus.

BAEP has begun to be universally applied for the evaluation of brainstem functions in neurological intensive care units, and the frequency of its use was only second to EEG in the present survey. BAEP is advantageous in that it is unlikely to be affected by the depth of sleep, and sedative agents that might affect EEG activity. BAEP has long been examined for the diagnosis of brain death in adults, and has also begun to be applied to pediatric cases.[53,72–75] However, it has been repeatedly

pointed out that caution must be exercised while interpreting BAEP in the state of brain death,[76,77] and currently available criteria rarely incorporate this test as an essential element.[55,56] Therefore, we do not recommend BAEP as an indispensable adjunctive test.

2) Short-latency somatosensory evoked potentials (SSEP)

Short-latency SSEP are usually recorded by leads at the right and left Erb points, skin on the cervical spinous processes, and the scalp, following electrical stimulation of the median nerve at the wrist. The wave pattern is evaluated in the state of brain death, in association with their origin. At the time of this writing, no brain death criteria anywhere in the world adopt SSEP, regardless of whether the subjects are adults or children, and the value of the test remains unestablished.[56] In particular, the significance of the P13-14 component in the recording from the scalp poses an unresolved issue. Although the application of the nasopharyngeal reference electrode[78] and the usefulness of the N18 component[79] have been reported in adults, there have been no related reports in children.

The recording of SSEP is also difficult in children, and often, obscure results are obtained even in normal cases. This probably explains why SSEP is not used for the determination of brain death in paediatric cases.

(2) Cerebral circulation

1) Cerebral angiography

(i) Intravenous digital subtraction angiography (IV-DSA)

To determine the cessation of cerebral blood flow by cerebral angiography based on a lack of visualization of vessels, IV-DSA is useful from the viewpoint of simplicity and popularity. The diagnostic ability of IV-DSA is said to be comparable to that of intra-arterial (IA)-DSA. Although rapid infusion of the contrast medium via the brachiocephalic vein is the most commonly employed method, the technique needs skill when used in children. An alternative method is dye infusion into the right atrium via the femoral vein, which, however, requires a higher volume of contrast medium. In neonates, aortic arch angiography via the umbilical artery is a simple method.

(ii) Dynamic CT

In this method, enhancement of intracranial blood vessels after rapid intravenous infusion of contrast medium is observed by CT to judge the cessation of cerebral circulation, similar to the case in cerebral angiography. This technique has a high resolving power, and allows enhancement of cerebral vessels even in cases of marked circulatory delay, and detects even very slight residual blood flow. In Japan, CT facilities are available widely, enabling easy application of this technique. Dynamic helical CT is a recommended technique which provides more accurate information within a shorter period of time. The area from the second cervical spine to the vertex is visualized and reconstructed about 20 sec or 1 min after rapid infusion of contrast medium into an antecubital vein, and circulatory arrest is determined by the absence of visualization of the circle of Willis and the peripheral arteries, the internal cerebral vein, the great cerebral vein of Galen, and the straight sinus.[80]

It must be added that while performing these procedures of cerebral angiography residual blood flow is not rare in neonates and infants with high intracranial pressure. Blood flow is often noted in the main stem of the cerebral arteries (A1, M1), and may represent retrograde filling via the anterior and posterior communicating arteries in children.[81] In addition, luxury perfusion after cerebral decompression should also be excluded. Although cerebral angiography is not indispensable for the determination of brain death,[82] it is a useful adjunctive examination.

2) Single photon emission CT (SPECT)

This technique has a high sensitivity and provides images of perfusion in the cerebellum and brainstem with considerable resolution. The radiopharmaceutical, Tc-99m-ECD, is a useful agent that provides a good contrast against the background and the results are not confounded by the presence of luxury perfusion.[83] Confirmed loss of cerebral perfusion is associated with a high frequency of brain death.[84] Slight perfusion may be found in the basal ganglia, thalamus, and brainstem in neonates and infants, which may be misleading.[84] This technique is simple and highly accurate, and may be recommended as an adjunctive qualitative examination technique for visualizing the total cerebral circulation.

3) Xenon CT

This procedure allows quantification of cerebral regional blood flow and is useful in pediatric cases. Although it is a useful adjunctive examination, particularly in patients receiving drugs in whom the diagnosis of brain death cannot be made established by clinical findings,[85] it is not yet used widely. Xe helical CT has yet to be established, and a blood flow map with only 3–4 slices is available. Determination of blood flow in the brainstem is difficult. A cerebral blood flow level of less than 5 m*l*/100 g/min is judged to be a lack of blood flow, considering the background noise,[85,86] and if it is apparent in the whole brain, it is a useful finding supporting the diagnosis of brain death.[86] Children aged 1 month old or older may remain alive with a cerebral blood flow level of 10–15 m*l*/100 g/min.[85] However, the ischemic threshold of the cell membrane is much lower in premature infants. Premature infants and neonates may survive under the conditions of low cerebral blood flow.[87,88]

Considering the simplicity and popularity of examinations of cerebral circulation as adjunctive tests, IV-DSA, dynamic CT, and SPECT may be considered useful. However, each of these examinations for determining cerebral circulation and metabolism has its own limitations. In practice, these techniques should be used with a full understanding of their limitations.

4) Doppler ultrasonography

As waveforms suggestive of cerebral blood flow arrest, countercurrents in diastole (oscillating flow; OcF) and spike waves in systole alone (systolic spikes) and loss of blood flow signals are widely accepted as findings specific to brain death in adults.[89,90] This can be applicable to older children. However, finding of cerebral blood flow arrest[89] based on the blood flow waveforms is not homonymous to loss of neurological function, i.e., clinical brain death[91] or loss of electrophysiological function,[52] and this limits the usefulness of the technique in the determination of brain death.[92]

In neonates and infants in whom the fontanelles are open, B mode allows easy anatomical evaluation, and cerebral hemodynamics in the state of brain death has been examined by this method.[93–95] The present survey revealed a relatively high rate of utilization of ultrasonography in pediatric neurological intensive care. However, in infants, particularly in neonates, this examination has limitations as an adjunctive test for the determination of brain death.

In children under the state of brain death, there are definitely different findings in intracranial and extracranial blood vessels.[93,96,97] Brain-dead infants less than 4 months old exhibit no typical OcF in studies of blood flow waveforms in the common carotid artery. So-called cerebral blood flow arrest[89] is also not noted.[98]

Ultrasonography is advantageous in that it is noninvasive and can be repeated at the bedside. However, this technique is not adequate, since findings may not be consistent due to the osseous transparency of the temporal bone, and technical skill is required to perform the test satisfactorily, besides the differences noted between intracranial and extracranial vascular findings.

Brain Death Criteria

1. Subjects

1) Patients in deep coma with apnea due to organic brain damage who require artificial ventilation.
2) Patients in whom the cause of the disease that may lead to brain death has been definitively diagnosed (diagnostic imaging by CT is essential).
3) Patients in whom it is judged that there is no possibility of recovery even after application of every therapeutic intervention currently available.

2. Exclusions

(1) By age
Less than 12 weeks of adjusted age

(2) By hypothermia and drug effects
1) Core temperature less than 35°C
2) Acute drug poisoning

(3) By disease
Metabolic disorders, endocrine disease
* If eye injury, middle ear injury, or high spinal cord injury partially precludes brainstem reflex or apnea testing, adjunctive tests such as brainstem auditory evoked potential recording and cerebral circulation tests may facilitate comprehensive determination of brain death.

3. Precautions During Determination

1) Blood pressure: hypotension unreasonable for age should be avoided.
2) When central nervous system depressants have been used, brain death should be diagnosed after the blood concentration of the drug has decreased to below the effective level as confirmed by measurement of the blood concentrations, and if possible, when muscle relaxants have been used, the absence of residual effects should be evaluated with a nerve stimulator as the occasion demands.

4. Essentials

(1) Consciousness
Deep coma
300 according to the Japan coma scale (3-3-9 method), or GCS 3

(2) Pupils
Bilateral mid position
Diameters 4 mm or greater

(3) Brainstem reflexes
Absence of light reflex
Absence of corneal reflex
Absence of ciliospinal reflex
Absence of oculocephalic reflex
Absence of vestibular reflex
Absence of pharyngeal reflex
Absence or cough reflex
Spinal reflex may be present.

(4) EEG
Electrocerebral silence (ECS)

Electrodes are placed at Fp1, Fp2, C3, C4, O1, O2, T3, T4, and Cz (10–20 International method) to cover a wide area of the cerebrum, and EEG recordings are obtained for at least 30 min with a reference electrode lead (6 leads) and bipolar leads (4–6 leads). The EEG is recorded at a higher sensitivity of 2μV/mm for a part of the recording.

(5) Respiration
Apnea confirmed by CO_2 challenge (apnea test)

Before the start of apnea test, it is desirable that the core temperature be 35°C or higher, the PaO_2 200 mmHg or higher, and the $PaCO_2$ 35–45 mmHg. The test is carried out while monitoring the blood pressure, ECG, heart rate and SpO_2.

After 10 min of artificial ventilation with 100% oxygen, the artificial ventilation system

is replaced by oxygenation with 100% oxygen (6 *l*/min) via a T-piece (Jackson-Rees system), and the patient is examined for respiratory movements by visual observation and chest auscultation. Observation is complete when the $PaCO_2$ reaches 60 mmHg or higher, and the test is judged to be positive if no respiratory movements are observed at that time.

Further accumulation of experience is desirable for cases with posterior fossa lesions.

5. Observation Period

24 h or more.

Conclusion

The present Study Group carried out a national survey to investigate brain death in children under 6 years of age, who were excluded from the purview of the criteria prescribed by the Study Group of the MHW. From the results of the survey, we developed new criteria for the determination of brain death in children. It is well known that brain damage in children is not a simple miniature of adult brain damage. However, the pathological state of brain death in children is similar to that in adults, and the criteria for the diagnosis of brain death in the pediatric age group were developed in accordance with the same concepts as those underlying the criteria prescribed by the MHW.

Criteria for the determination of brain death in children are limited internationally. Among those, the criteria published by the US Task Force in 1987 are representative. The important differences between both their criteria and ours are as follows: children under 12 weeks of age (adjusted age) are excluded, EEG is essential, and the observation period is longer in our criteria.

The criteria developed by the present Study Group are rigid from the international viewpoint. Although the basic concept of brain death remains unchanged, it is possible that adjunctive tests may improve along with advances in medical technology. It is hoped that the criteria proposed by us will be further refined by accumulation of data and constructive criticism of this document.

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