

EXPERIENCE AND REASON—Briefly Recorded

"In Medicine one must pay attention not to plausible theorizing but to experience and reason together. . . . I agree that theorizing is to be approved, provided that it is based on facts, and systematically makes its deductions from what is observed. . . . But conclusions drawn from unaided reason can hardly be serviceable; only those drawn from observed fact." Hippocrates: *Precepts*. (Short communications of factual material are published here. Comments and criticisms appear as letters to the Editor.)

Return of Spontaneous Respiration in an Infant Who Fulfilled Current Criteria to Determine Brain Death

ABBREVIATIONS. EEG, electroencephalogram; ADH, antidiuretic hormone; CT, computed tomography; BAER, brainstem auditory-evoked response.

It is generally assumed that the child's brain is more resistant to insults leading to death. Current guidelines for brain death, therefore, avoid application of these standards to young children.¹ The determination of brain death in children, however, has become increasingly important, and different sets of new guidelines for children have been recently published.¹⁻⁴ Especially, the recommendations of a special task force, consisting of representatives from neurologic organizations and the American Academy of Pediatrics, were published in five major journals.⁴ Those primary distinctions were three separate longer observation periods depending on the child's age and the necessity for two corroborating electroencephalograms (EEGs) or one EEG with a corroborating cerebral radionuclide angiogram. On the other hand, counterexamples in which certain infants seem to recover after fulfilling the criteria are open to question in any guidelines, but they have been seldom reported with precisely examined data. Now many authors have agreed that, except in very immature newborns, the same criteria of brain death should apply to full-term newborns, infants, children, and adults.⁵

We report a 3-month-old girl with hypoglycemia caused by nesidioblastosis who fulfilled the current criteria for brain death but who regained her spontaneous respiration more than 5 weeks later. Radiologic evaluations demonstrated preservation of cerebral perfusion for a prolonged period, and neuroendocrine assessments demonstrated an obvious remnant of some hypothalamohypophysial function. Criteria for brain death in children still remain controversial. Our extremely unusual case should be carefully considered in the determination of brain death in young children.

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CASE REPORT

This 3-month-old girl had been born at term by normal delivery and seemed healthy before the accident. She was discovered to be apneic during her midday nap. Although cardiopulmonary resuscitation was immediately begun by her mother, the cardiac arrest was recognized 5 minutes later when paramedics arrived. The patient was taken to a local hospital, where successful cardiopulmonary resuscitation was performed; she regained a sinus heart rhythm and then regained spontaneous respiration 40 minutes later. She was transported to our tertiary care facility.

On admission the infant was deeply comatose and dehydrated. Transient hypotension existed and improved with infusion of electrolytes and colloids. Neither catecholamines nor antidiuretic hormone (ADH) was required to maintain the hemodynamics. She had equal and reactive pupils (diameters of 2.5 mm) and intact brainstem reflexes, which were induced by oculocephalic, caloric, and gag testing. Her spontaneous respiration was regular with a rate of 30 to 35 breaths per minute. The anterior fontanelle was open and slightly bulged. The extremities were spastic with bilateral Babinski signs, and decerebrated posturing was observed with pinprick stimulation. She was hypothermic, with a body temperature of 34.8°C and was warmed by an electric blanket. Laboratory testing showed the presence of persistent hypoglycemia (blood glucose level <30 mg/dL). Continuous administration of glucose at a rate of 9 mg/kg per minute was required to maintain a normal blood glucose level. This hypoglycemia was proved by a glucagon test to be caused by hyperinsulinemia. The other laboratory data were almost within normal limits. She had no prodromes of respiratory tract symptoms before the accident and no clinical findings suggesting infectious diseases such as encephalitis. Because the initial intensive care improved her systemic circulation and hypoglycemia, the following dehydration therapy was done to prevent the aggravation of cerebral edema. An appropriate dosage of 20% glycerin and lactated Ringer's solution with 20% glucose was infused.

Despite supportive measures, improvement of hypoglycemia and hypothermia, no hypotension, and no use of sedative or hypnotic drugs, the infant's neurologic condition gradually deteriorated. On the second day in the hospital (day 2), her respiration was completely synchronized with the respirator. Her pupils grew dilated and were fixed in the midposition, and then presence of corneal and gag reflexes became unclear. Computed tomography (CT) revealed the presence of a mild cerebral edema and revealed the absence of herniation, a focal hemorrhage, and other lesions. The whole brain was well enhanced in a contrast CT. Brainstem auditory evoked responses (BAERs) showed a bilateral presence of waves I through V. On day 3, the physical examinations revealed a deep coma, fully dilated pupils (diameters of 6 mm) that did not respond to light, and the absence of corneal, gag, cough, sucking, and rooting reflexes. No eye movements were induced by oculocephalic and caloric testing. She had a flaccid tone, no spontaneous movements, and no movements elicited by painful stimulation. There was no bulge of the anterior fontanelle. The absence of spontaneous respiration was determined by an apnea test (PCO₂ of 69.3 mm Hg). An EEG was performed in accordance with the standards of the American Electroencephalopathy Society.⁶ The record was taken during a 30-minute period, and the gain was at the setting of 5 to 10 µV/mm. Two neurologists evaluated the EEG in detail, and both of them agreed that it was consistent with electrical cerebral silence. On day 5, after 48 hours of observation, neurologic examinations were repeated and remained unchanged. An apnea test performed again demonstrated the absence of respiratory response to PCO₂ of 62.1 mm Hg. An EEG revealed no

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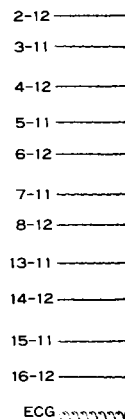


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electrical activity (Fig 1). BAERs showed bilateral loss of all components. At that point, the patient was diagnosed as brain dead according to the current guidelines, including those of the Task Force. However, supportive measures to her were continued, because brain death in infants has not yet been accepted as legal death in Japan. She only received an infusion of 20% glucose at 600 mL/day and continuous enteral feeding afterward. The hemodynamics were kept stable for the next 2 months with no vasoactive drugs such as catecholamines or ADH. On days 7, 14, and 21, neurologic examinations excluding apnea tests, EEGs, and BAERs were repeated and continued unchanged. On day 19, a CT with contrast demonstrated remarkable atrophy of the cerebral cortex but demonstrated cerebral blood flow in the whole brain (Fig 2). On day 22, four-vessel cerebral angiography disclosed almost normal visualization of the cerebral circulation (Fig 3). From days 27 to 33, endocrine assessment was performed to evaluate hypothalamohypophysical function. By the infusion of 250 µg of thyrotropin-releasing hormone, the plasma thyroid-stimulating hormone level rose to 11 mU/L. Hypoglycemia induced by the infusion of 0.3 U/kg insulin significantly stimulated the secretion of plasma adrenocorticotropic hormone and plasma cortisol as twice as the base line. The infusion of 0.3 U/kg insulin or 0.5g/kg arginine failed to increase the serum growth hormone level. A water deprivation test revealed an obvious increase of the urine osmolality and the plasma ADH level. Urine and plasma osmolality reached more than 2, and urine output decreased after 16 hours of water deprivation. The relationship of plasma osmolality and ADH secretion was delineated.

There was little change in the infant's condition until day 43, when she regained spontaneous respiration. The respiration irregularly occurred at a rate of two to three breaths per minute and with a tidal volume of 40 to 50 mL. The arterial blood gases when the respiration recurred revealed a PO₂ of 122.5 mm Hg, a PCO₂ of 30.1 mm Hg, and a pH of 7.35. Neither the stimulation with an apnea test (PCO₂ of 73.5 mm Hg maximally) nor infusion of 20 mg of doxaplam increased the rate of spontaneous respiration and tidal volume at all. The other neurologic signs including brainstem reflexes and ancillary tests of EEGs and BAERs were carefully examined, and those results remained unchanged. The irregular spontaneous respiration had continued until day 71, when she died of pneumonia. At autopsy, the structure of the whole brain was preserved. There was no cerebral liquefaction like a "respirator brain." Light microscopic findings revealed total necrosis in most of the gray matter, including layers of the cerebral cortex and medulla of the brain stem. The white matter had its preserved structure though nuclear pyknosis and chromatolysis, and a hardly stainable cell shadow (ghost cell) was frequently observed. The changes in the cerebellum were relatively mild. The histologic appearance of nesidioblastosis⁷ was seen in the pancreas.

DISCUSSION

Before certification of brain death, the proximate cause of coma must be determined, and irreversibility of the disorders must be confirmed. Almost all the

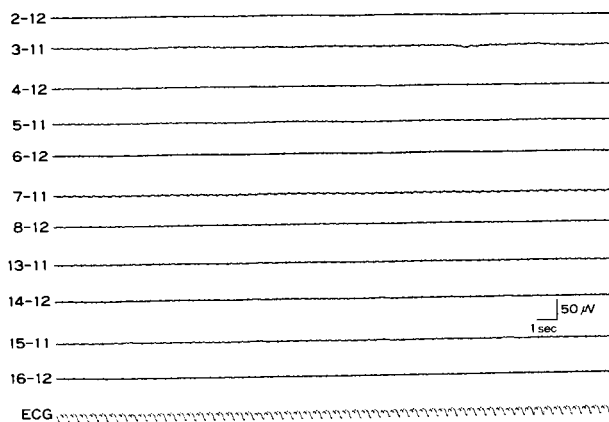


Fig 1. EEG after 48 hours of observation demonstrates electrocerebral silence; S = 5 µV/mm; high-cut filter, 120 Hz.

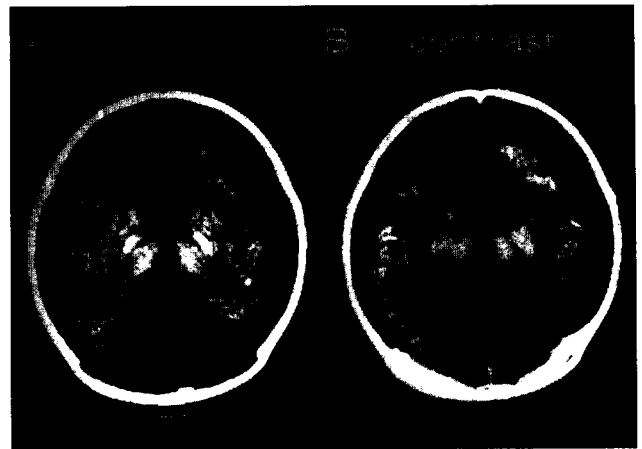


Fig 2. A, CT on day 19 demonstrates marked cerebral atrophy of the supratentorial gray and white matter. B, Contrast-enhanced CT on the same day demonstrates evidence of cerebral blood flow.

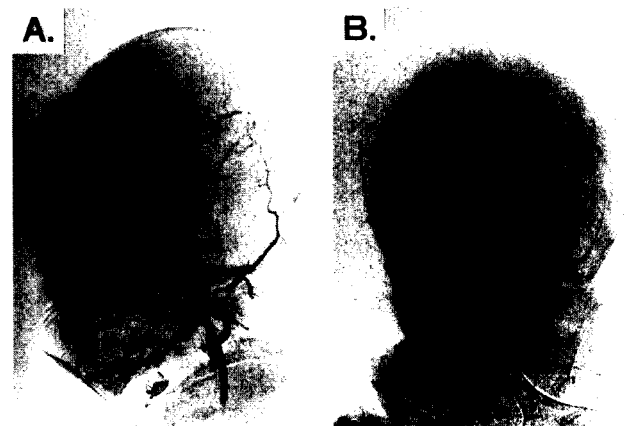


Fig 3. Contrast angiography on day 22 demonstrates normal visualization of the cerebral circulation. A, Left carotid angiogram, lateral view; B, left vertebral angiogram, anteroposterior view.

guidelines, therefore, list examples of potentially reversible conditions, such as metabolic disorders, a drug-induced coma, and hypothermia. In our case, severe hypoglycemia caused by hyperinsulinemia is suggested to have caused unexpected apnea. Histologic evidence proved pancreatic nesidioblastosis, which is one of the major causes of infant hyperinsulinemia,⁷ and which possibly can cause unexpected apnea or sudden death in infants. Our patient's brain would be severely damaged by insults of both hypoglycemia and anoxia. Hypoglycemia was immediately corrected, and the absence of other reversible or remediable conditions was confirmed in the determination of brain death.

Neurologic examinations and EEGs fulfilled the current criteria to determine brain death in our patient. According to the task force's guidelines, she was diagnosed as brain dead on day 5. However, we thought that she was different from typical brain-dead patients. First, her cerebral injury was caused neither by trauma nor hemorrhage, but by metabolic disorders of hypoglycemia and hypoxia. Second, delayed neurologic deterioration occurred in the absence of intracranial hypertension caused by massive cerebral edema. Third, there was no sequential

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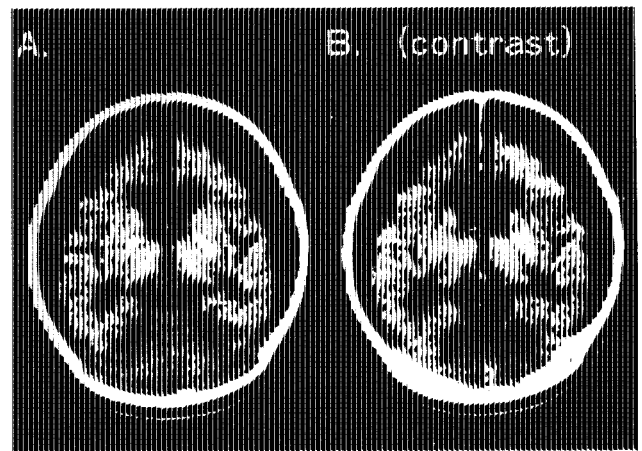


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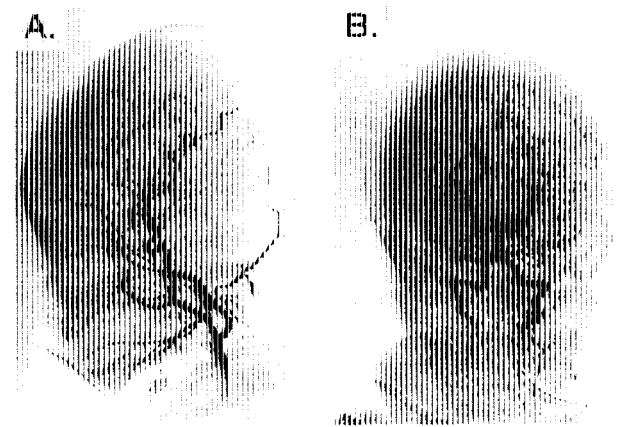


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circulatory deterioration, which usually occurs soon after brain death. Therefore, she was treated with extreme caution, and the additional ancillary tests were performed after the determination of brain death. Both CT and angiography on days 19 through 22 showed presence of the whole cerebral vascularity and nearly normal perfusion. Results of an assessment of hypothalamohypophysical function revealed not only secretion of pituitary hormones, but also evidence of regulations or feedback actions of pituitary hormones. We concluded that this patient had some remnant of hypothalamohypophysical function. Surprisingly, our patient regained spontaneous respiration on day 43, more than 5 weeks since the determination of brain death. The spontaneous respiration was insufficient to remove the respirator, and it did not respond to stimulation by a high level of P_{CO_2} or doxapram. Irregular bradypnea and no response to both peripheral chemoreceptor stimulation with a high level of P_{CO_2} and direct stimulation of medullary neurons with doxapram⁸ suggest disorders of both the dorsal portion of the medulla, which controls the basic rhythm of respiration, and the pneumotaxic center of the pons, whose signal can increase the breathing rate.⁹ The central regulatory mechanism for respiration is complex, because several neural components are involved in the respiratory center located bilaterally in the medulla oblongata and pons, and the central mechanism itself is modulated by many inputs from peripheral chemoreceptors.⁹ Although damaged areas of respiratory centers were not clearly confirmed, it was unquestionable that she was not brain dead. Autopsy findings also were not consistent with brain death.

It is emphasized by Kohrman and Spivack¹⁰ that criteria for brain death must be both sensitive and specific. Although a lack of sensitivity will increase both the financial cost for prolonged maintenance therapy and the loss of organs appropriate for transplantation, the lack of specificity implies a more serious problem, because irreversible absence of all brain stem functions is a cornerstone in the diagnosis of brain death. Although, to our knowledge, there is no published data or documentation about the counterexamples against current criteria, those rare examples surely exist. A previous report by Pasternak and Volpe¹¹ demonstrated that a 35-week-old premature infant with an intraventricular hemorrhage who had total brainstem failure for 3 days survived with only a mild development delay, although the EEG activity was present. Another 6-week-old infant with seizure and apnea had both the absence of brain function and a flat EEG but recovered both function and EEG activity the following day.¹² Kohrman and Spivack¹⁰ reported a 3-month-old infant with encephalitis who fulfilled the task force's criteria but regained partial cortical and brainstem function the following day, and they asserted the necessity of prolonged observation before the diagnosis of brain death. Those examples show that young children are more likely than adults to survive severe brain insults, and therefore, we do not consider that the same criteria of brain death should apply to young children and adults. And we question whether new guidelines,

including those of the task force, are more reasonable, because evidence from our case demonstrates that the problems of criteria do not involve only the inappropriateness of the observation period. We suggest that the cause of a brain insult may be more arguable in the diagnosis of brain death. In our case, hypoglycemia would be the most important and responsible insult for the infant's unusual clinical course. We think that extreme caution is necessary when considering brain death from metabolic and toxic causes.

According to a recent review by Farrell and Levin,⁵ there are a variety of tests used to document brain death, but no test is absolutely confirmatory of brain death and can only be consistent with the diagnosis, with the possible exception of a four-vessel cerebral angiography showing no cerebral blood flow. Non-filling cerebral angiography may be irrefutable evidence of brain death, although the converse is not true. We consider that cerebral angiography should be aggressively performed, except when self-evident signs exist such as a massive cerebral contusion or completed rostral-caudal herniation. Especially in a case that requires caution, one confirmatory angiogram is indispensable for the determination of brain death in children. Technical problems with the procedure of angiography should not render it impractical for clinical use.

Criteria for establishing brain death in children still remain controversial. We hardly consider that brain death cannot be diagnosed in infants, but we think that extreme caution should be used in the diagnosis. Our unusual case must be carefully considered in the determination of brain death in young children.

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