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ABSTRACT

Background: Autopsy studies in patients who have been declared brain dead are rare. Total brain necrosis ("respirator brain") has been a common finding in the distant past. The time to brain fixation has been shortened as a result of timely organ transplant protocols, therefore the neuropathologic findings may be different than previously described.

Methods: We reviewed macroscopic and microscopic brain pathology for ischemic neuronal damage in 41 patients who fulfilled the clinical criteria of brain death. Hematoxylin and eosin stained brain tissue slides were retrieved and available wet tissue was additionally stained to complete a series of samples of the hemispheres, brainstem, and cerebellum for each patient. Neuronal ischemic change was semiquantitatively graded for severity (mild 0 to 5%, moderate >5 to 75%, and severe >75%).

Results: After the clinical diagnosis of brain death and terminal cardiac arrest, 12 brains were fixated in less than 12 hours and 29 brains were fixated between 12 and 36 hours. The frontal lobe, temporal lobe, parietal lobe, occipital lobe, and basal ganglia showed moderate to severe ischemic change in 53 to 68% of the cases. Moderate to severe neuronal ischemic change was found in the thalamus in 34%, midbrain in 37%, pons in 41%, medulla in 40%, and cerebellum in 52% of the cases.

Conclusions: No distinctive neuropathologic features were apparent in our series of patients with brain death. Neuronal ischemic changes were frequently profound, but mild changes were present in a third of the examined hemispheres and in half of the brainstems. Respirator brain with extensive ischemic neuronal loss and tissue fragmentation was not observed. Neuropathologic examination is therefore not diagnostic of brain death. ***Neurology*® 2008;70:1234–1237**

GLOSSARY

ICH = intracerebral hemorrhage; **SAH** = subarachnoid hemorrhage.

Brain death is a precisely defined clinical diagnosis. Invariably, a catastrophic injury has led to irreversible coma with absent brainstem reflexes and apnea. Mostly, increased intracranial pressure is the main mechanism of brain death, and intracranial blood flow stagnates and eventually stops. Maintenance of hemodynamics and oxygenation using vasopressors, vasopressin, and high positive end expiratory pressure mechanical ventilation can support somatic organs and allow ongoing brain necrosis. In the distant past, neuropathologists have noted particular characteristics in these supported brain dead patients and coined the term "respirator brain."[1-3] The typical features at autopsy were a dusky congested discolored brain containing liquid portions and often the brain fragmented when removed from the calvarium.[4] Although areas of the brain were preserved, neuronal injury was generally extensive and commensurate with the clinical findings.[5,6]

Autopsy studies in patients who have been declared brain dead have been infrequently reported. In addition, due to the implementation of prompt organ harvesting programs, the time to autopsy has been remarkably shortened, and therefore, early preservation of the brain

Editorial, page 1230

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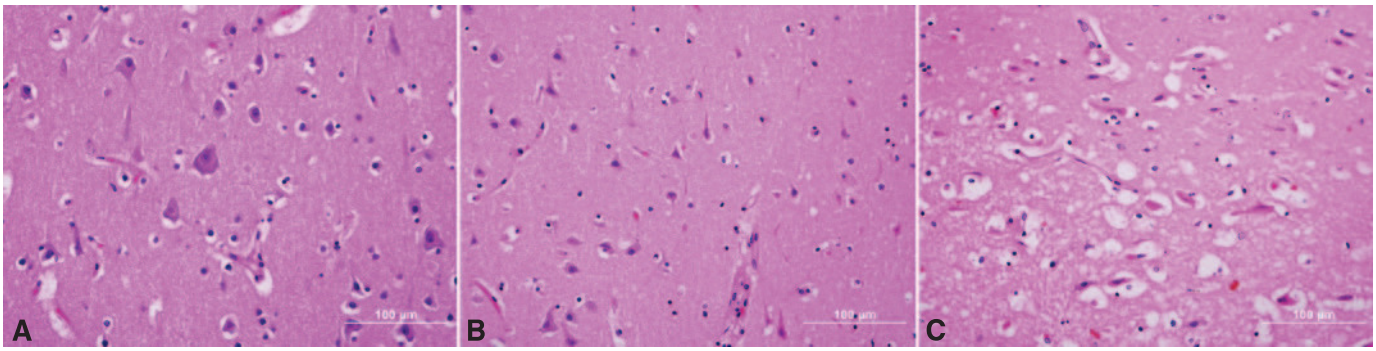
Figure 1 Neuronal ischemic changes



(A) Normal appearing pyramidal neurons. (B) Scattered neurons with ischemic changes, including contracted, hypereosinophilic cytoplasm and nuclear changes. (C) Diffuse ischemic changes.

should affect the neuropathologic findings.[7] Moreover, how much necrotic brain tissue is present in clinically brain dead patients has been an area of contention and some have allowed surviving nests of neurons.[8] We report an autopsy series of brain dead patients in the modern transplant era.

METHODS From 1999 to 2005, 43 neuropathologic examinations were granted in 168 (25%) patients who became brain dead. We excluded two children. The medical records of 41 patients were reviewed and we obtained data on diagnosis, craniotomy for removal of mass effect or for treatment of intractable intracranial pressure, time of brain death determination, time of cardiac arrest, and the need for vasopressors or vasopressin. All patients fulfilled the clinical criteria of brain death according to practice guidelines of the American Academy of Neurology.[9] This included specific attention to confounding conditions, documentation of absent brainstem reflexes, and a formal apnea test procedure.

Table Clinical features of 41 patients progressing to brain death with available autopsy material

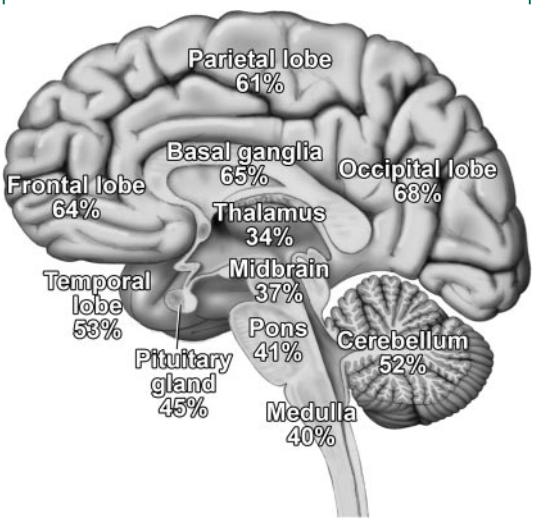
Characteristic	Total no.
Median age, y (range)	27 (19–80)
Male sex	30
Cause of brain injury	
Trauma	33
SAH	3
ICH with mass effect	2
Cardiac arrest	2
Stroke with swelling	1
Cardiopulmonary resuscitation	4
Emergency craniotomy	2
Time from initial injury to brain death, h	
0–24	27
24–48	5
>48	9
Brain death to cardiac arrest, h	
0–12	12
12–24	4
24–36	25

SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage.

The brains were fixed in 10% formalin before neuropathology evaluation. Routine hematoxylin and eosin stained brain tissue slides of fixed brains were retrieved from archival storage and available wet tissue was taken to complete a series of samples for each patient. Each frontal lobe sample contained right or left superior medial frontal gyrus. Temporal lobe sections consisted of randomly obtained coronal samples. Coronal sections of the thalami, basal ganglia, and hippocampi were obtained. Transverse sections of the brainstem included the mesencephalon, pons, and medulla oblongata. Transverse sections of the cerebellum included cortex and dentate nuclei. All slices were reviewed by a forensic pathologist (E.A.P.) without knowledge of the diagnosis and clinical course. Brain samples were reviewed for neuronal ischemic change and semiquantitatively graded as mild (0 to 5%; figure 1A), moderate (>5 to 75%; figure 1B), or severe neuronal loss (more than 75%; figure 1C). Pyramidal neurons were considered irreversibly damaged when shrinkage, aggregated chromatin, or increased eosinophilic staining was present. Specific attention was paid to the Purkinje cells and CA_1 region of the hippocampus.

RESULTS The clinical characteristics are summarized in the table. The age of the patients varied from 19 to 80 years (median of 27 years). Brain death was declared within 24 hours after the initial brain injury in two thirds of the patients. Only two patients had an emergency craniotomy. In four patients, acute brain injury was associated with cardiopulmonary resuscitation. The cause of brain death was traumatic brain injury in 33 patients, ischemic and hemorrhagic stroke in 6 patients, and cardiopulmonary resuscitation for primary cardiac arrest in 2 patients. All patients were supported by IV infusions of dopamine or norepinephrine. Vasopressin was administered in 33 of 41 (81%) patients. Temperature, arterial

Figure 2 Percentage of moderate to severe neuronal ischemic changes in 41 autopsies of patients who fulfilled the clinical criteria of brain death



PCO_2, and PO_2 were maintained within normal values after the clinical diagnosis of brain death. Six patients with absent brainstem reflexes underwent confirmatory laboratory tests (EEG, cerebral angiogram). In all these six patients the apnea test had to be aborted due to a brief hypotension and hypoxemia after disconnection from the ventilator. Cardiac arrest occurred within 36 hours either after withdrawal of support or at the completion of organ harvesting. The time to fixation of the brain from declaration of brain death was within 0 to 12 hours for 12 patients and within 12 to 36 hours for 29 patients.

Neuropathologic findings. The brain weighed 830 to 2,010 g (median 1,515 g) and was increased in all patients compared to age and gender norms. Diffuse axonal injury and multiple contusions were identified in patients after traumatic head injury. Destructive hemorrhagic stroke and ischemic strokes with mass effect was confirmed on macroscopic views. Microscopic evaluation revealed varying degrees of neuronal ischemic changes in the reviewed samples (figure 2). The hemispheric lobes and basal ganglia showed moderate to severe neuronal ischemic changes in 53 to 68% of the samples. Moderate to severe neuronal ischemic changes were found in the thalamus in 34%, midbrain in 37%, pons in 41%, and medulla oblongata in 40%.The cerebellum showed tonsillar herniation and moderate to severe neuronal ischemic changes in the granular and Purkinje cells in 52% of the samples. Autolysis of the cerebellum was noted in 6 patients. In addition, 31 brains could be examined for hippocampal damage with moderate to severe neuronal ischemic changes in 23 tissue samples. The pituitary gland showed variable damage in the anterior lobe but moderate to severe neuronal loss was found in 45% of 16 examined pituitary glands. Both patients with cerebral edema after primary anoxic-ischemic injury had severe neuronal necrosis in all hemispheric samples, but moderate neuronal ischemic changes in the brainstem.

DISCUSSION Cerebral edema raises pressure in the intracranial vault and inexorably results in a nonperfused brain when intracranial pressure exceeds diastolic blood pressure. Total necrosis may appear macroscopically as a dusky gray–brown cerebrum and parts may disintegrate at autopsy. Traditionally, the herniated swollen cerebellum is affected early and tonsils can fragment into pieces that could become displaced in the intrathecal space.[4] Apart from the cause of injury, microscopic findings show disappearance of neuronal cells but also less profound abnormalities consisting of cloudy swelling and loss of basophilia.[10] White matter may contain perivascular hemorrhages and axonal balloons.[10,11]

The largest study on neuropathology in brain death came from the Collaborative Study of Cerebral Death directed by Walker and included 226 brains.[1] In 94% of the examined brains the cerebral cortex showed "pericellular edema, necrosis, neuronal loss and infarction." The basal ganglia and diencephalon were less affected. No inflammatory or cellular reaction was noted consistent with circulatory arrest in the brain, setting it apart from anoxic-ischemic encephalopathy with common tissue reaction.[4,12-14]

Our series confirms widespread ischemic neuronal changes throughout the brain. These ischemic changes are expected because the most common mechanism of brain death in our series was due to intracranial pressure resulting in arrested flow. Nonetheless, sporadically appearing ischemic neuronal loss was found in approximately a third of the brain lobes, a third of the thalami, and in about half of various regions of the brainstem. Infarction of the pituitary was less common than previously reported despite its vulnerability due to interruption of hypothalamic portal venous blood. Sparing of the pituitary gland may also be explained by the rich arterial supply provided by the extracranial carotid arteries unaffected by cerebral swelling.

It has been recognized that time on the ventilator—a reflection of time with no cerebral blood flow—correlated with autopsy findings. In a

prior study respirator brains were rarely observed when fixation occurred within 12 hours of cardiac arrest increasing to 50% of nonperfused brains kept on the ventilator between 14 and 48 hours.[14] In our series early fixation of the brain likely impacted on the neuropathologic findings, because organ harvesting for donation occurred in less than 36 hours with a third less than 12 hours after the clinical determination of brain death.

The most severe diffuse neuronal damage was found in two patients after cardiac arrest. This confirms the devastating impact of anoxic ischemic injury to the brain and in particular when it leads to loss of all brain function. The frequency of thalamic necrosis was much lower than expected. A recent neuropathology study in persistent vegetative state after traumatic brain injury found thalamic injury in 80% of examined brains.[11] Our study also largely consisted of patients with traumatic brain injury and thus the frequency of thalamic injury after trauma may be different between patients in persistent vegetative state and patients who progressed to brain death.

We recognize limitations with the use of routine staining methods and more specific stains may have uncovered more cellular injury or apoptosis. Although neuronal loss is widespread, total brain necrosis is not observed. We found no prototypical examples of a respirator brain, therefore, our study has important consequences in forensic cases. As in other comatose states such as a persistent vegetative state or minimally conscious state, the neuropathologic findings lack sufficient distinctive characteristics, and the diagnosis of brain death therefore should be based on clinical assessment alone. Although the existence of a separate entity such as the respirator brain has not been reconciled, with the virtual disappearance of total brain necrosis it has become much less likely for the neuropathologist to confirm brain death.

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