

Brain Death or Brain Dying?

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For the past 50 years, the medical profession has understood “brain death” to represent the endpoint of a neuropathologic vicious cycle. An initial major brain injury sets off a mutually exacerbating cascade of cerebral edema, increased intracranial pressure, and decreased cerebral blood flow, which advances beyond some point-of-no-return to a state of no cerebral blood flow and total brain infarction (death of the brain, or “brain death”). This pathophysiology was considered so well established that the Swedish Committee on Defining Death chose that very term—“total brain infarction”—as its official name for the condition, avoiding the semantic ambiguities inherent in the term “brain death.”^{1,2}

Regardless of the name, this endpoint has been traditionally understood to correspond to brain-based statutory definitions of death everywhere in the world. In the United States, virtually all states have adopted some variation on the Uniform Determination of Death Act proposed by the President’s Commission in 1981, namely: “irreversible cessation of all functions of the entire brain, including the brain stem.”³ In clinical practice, both the irreversibility and totality of nonfunction are considered established by inference from sure knowledge that the neuropathologic vicious cycle has already reached its endpoint of no intracranial blood flow and total brain infarction. The past several decades have witnessed a search for practical clinical criteria to guarantee this inference in individual cases. Most developed countries have standardized protocols, which continue to evolve, although important controversies remain.⁴⁻⁷

But reality is rarely as straightforward as theory. In this issue of the *Journal of Child Neurology*, Suzuki and colleagues⁸ present evidence that “total brain necrosis might not be present in children at the time of clinical diagnosis of brain death.” Their hospital routinely follows serial serum levels of neuron-specific enolase, a standard marker of neuronal cell death, in children admitted with acute brain injuries. In a retrospective review spanning 14 years, the authors found 3 children who met clinical criteria for brain death following cardiopulmonary arrest and survived more than 2 months. For comparison, they selected 3 cases with cardiopulmonary arrest and poor outcomes short of brain death.

If the vicious cycle ending in total brain infarction universally plays itself out over the course of hours or a few days at most, and if the clinical diagnostic criteria reliably determine that the endpoint has already been reached, then one would

expect serum neuron-specific enolase levels to reflect an initial massive outpouring of neuron-specific enolase, followed by rapid exponential decay due to cessation of both intracranial blood flow and cerebrospinal fluid production and flow.

The investigators report three findings: two interesting but not surprising, and one very surprising. (1) The children with brain death had higher peak neuron-specific enolase levels than the controls. (2) The time to peak neuron-specific enolase level was not significantly different between the groups (4-10 days vs 5-8 days). (3) Remarkably, all 3 children with brain death had persistent elevation of neuron-specific enolase at 4 weeks (>400 ng/mL) and 8 weeks (>50 ng/mL), in contrast to the two control survivors in the vegetative state, whose neuron-specific enolase decreased to <50 ng/mL within 4 weeks.

The authors acknowledge the study’s obvious limitations resulting from its retrospective methodology and the small number of patients that was insufficient for statistical power. They also point out that in the context of brain death, the time course of serum neuron-specific enolase might not exactly reflect that of neuronal cell death. An additional caveat not mentioned in the article is that the patients with chronic brain death they followed may not be (and probably are not) representative of all patients with brain death, particularly those that systemically deteriorate to asystole within a few days despite all therapeutic measures. The study needs to be replicated and extended, although that is much easier said than done. Clearly, this is a wide-open new area for clinical research, for which Japan is uniquely suited, as it is probably the only country where extended intensive care unit support of patients with brain death still occurs, out of respect for traditional societal values.

The neuron-specific enolase findings reinforce and contribute a novel temporal dimension to the growing neuropathologic evidence that at the time of fulfillment of clinical brain death criteria, the brain infarction may be far from “total.”^{9,10}

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The picture that seems to be emerging is that in at least some cases (perhaps many), the vicious cycle does not follow a spatiotemporally homogenous course, but rather occurs in a patchwork fashion, with regions of no-flow and necrosis interspersed with regions of some flow and relative preservation; and among the latter, the timing and rate of progression to no-flow probably varies.

The obvious next question is whether, at a given point in time, any of the non-necrotic areas has any function and, if not, whether the functional loss is irreversible (as stipulated in statutory definitions of death) or potentially reversible. It has long been recognized that in some cases of clinically diagnosed brain death, certain brain structures may not only be preserved but actually function, such as the hypothalamus (in cases without diabetes insipidus),⁴ relay nuclei mediating evoked potentials,^{11,12} and cerebral cortex mediating electroencephalographic activity.¹³ (Whether all such functions are of teleological significance to the organism as a whole is a separate question; they are certainly functions of those brain structures.) Acute hypotension requiring pressor medication generally accompanies brain death, because of damage to medullary vasomotor centers¹⁴; nevertheless, the American Academy of Neurology practice parameter explicitly states that the diagnosis of brain death is compatible with spontaneous cardiovascular stability.⁴ Hypertension in a minority of patients with brain death has been attributed possibly to “lingering function of caudal medulla pressor areas.”¹⁵ So there are already well-known precedents for preserved brain functions in clinically diagnosed brain death.

The Suzuki et al study⁸ and the neuropathology studies invite taking this consideration a step further. They lend credence to (though by no means prove) the “global ischemic penumbra” hypothesis advanced by Coimbra.¹⁶ It is a mathematical necessity that during the course of progression from normal blood flow to no blood flow, a given brain area must pass through a range of diminished flow insufficient for function but just sufficient for tissue viability, that is, the range called in the stroke literature the “ischemic penumbra.” During the window of time that blood flow is in the penumbra range, clinical and electrophysiological tests of function will be negative, yet the functional loss is in principle reversible. This is the whole basis for therapeutic efforts in stroke. What if the entire brain or large parts of it were for a time in the ischemic penumbra? The clinical criteria for brain death as well as electrophysiological “confirmatory” tests would be fulfilled, but the functional loss would not yet be irreversible. Even tests of cerebral blood flow could be misleading, given that none of the standard “confirmatory” tests for brain death has been validated to possess sufficient sensitivity to reliably distinguish penumbra-level flow from no flow, particularly in the posterior fossa.

The disconnect between statutory definition and neurologic reality is disturbing enough, but even more disturbing is the consideration that an apnea test, complicated by a bit of hypotension and/or acidosis, could be all it takes to precipitate a transition from penumbra-level perfusion to no perfusion.

Thus, the final step in the clinical algorithm for diagnosing brain death could, in an unknown (and intrinsically unknowable) proportion of cases, actually be the coup de grace that brings about the very totality and irreversibility that it purports to identify, without any externally observable sign that a self-fulfilling prophecy has just taken place. Given that the standard diagnostic criteria do not even make apnea testing an absolute requirement⁴ (in Wijdick’s series of 228 brain death cases, 7% had no apnea test and 3% had an aborted, incomplete test¹²), it is difficult ethically to justify such a test, which has no potential benefit for the patient but only risks. The risks typically discussed in the literature have been of the systemic variety (hypotension, hypoxia, acidosis, arrhythmias, etc.¹⁷), but the neuron-specific enolase and neuropathology data suggest that an additional category of risk could be that of unwittingly causing rather than merely diagnosing the total brain infarction, as Coimbra and Joffe et al have warned.^{18,19} The latter authors offer yet additional cogent reasons for abandoning the apnea test.¹⁹ At the very least, the apnea test is a procedure that by most hospital standards, ought to require explicit informed consent.

In summary, the neuron-specific enolase data of Suzuki and colleagues⁸ provide a new, independent line of evidence that what the clinical diagnostic criteria for brain death identify is, in some instances at least (perhaps many), not so much a state as an ongoing process. Whether that process, at the time of diagnosis, is already beyond the point of no return throughout the brain, or there might be areas of ischemic penumbra that are potentially salvageable through advances in intensive therapy (not to speak of areas that are overtly functional)—and if so, whether it would be ethically appropriate to attempt to rescue someone from impending brain death to a life with high risk of vegetative state or very severe disability—are critical and unanswered questions. Given the complex interplay in most Western countries between health care economics and pressures to increase the supply of transplantable organs, it is likely that Japan will play an increasingly important role in the scientific study of brain death.

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