An elusive brain death diagnosis: You can't get there from here

Nitin K. Sethi, MD: I read with great interest the case report by Story and Winter.¹ Their patient was brain dead clinically but confirmatory testing in the form of CT angiography and EEG was requested, which failed to document whole-brain death. One might argue that they would not have encountered this medical, ethical, and legal quandary if the concept of brain stem death was adopted and accepted universally as opposed to whole-brain death, which is the currently accepted criterion in the United States. Electroencephalographic inactivity or electroencephalographic silence in a brain death EEG is defined as no EEG activity over 2 μ V when recording from scalp electrode pairs 10 or more cm apart with interelectrode impedances under 10,000 Ohms (10 KOhms) but over 100 Ohms. It is a well-known fact that pockets of brain activity may persist in a patient who is clinically (all brain stem reflexes absent and apnea test positive) brain dead. These islands of brain activity may yield a false-negative brain death EEG, creating the confusion that the authors encountered. The diagnosis of brain death was never elusive; it was the unnecessary testing that made it so.

New York-Presbyterian Hospital.

Disclosures: N. Sethi serves as Associate Editor for *The Journal of Eastern Medicine*.

Elco F. M. Wijndicks, MD, David M. Greer, MD: Story and Winter's case report¹ contributes to the misunderstanding that ancillary tests can resolve a clinical examination in a pharmacologically confounded patient with an unsurvivable cerebral hemorrhage. Inexplicably the authors proceeded with a full brain death examination, knowing the patient did not meet the first and most important prerequisite of the American Academy of Neurology (AAN) guideline—to exclude confounders and determine eligibility for a full examination, including an apnea test.² The authors then missed the opportunity to proceed with a donation after cardiac death procedure. Subsequently, they again went in direct violation of the AAN guidelines by performing an unvalidated ancillary test. CT angiography (CTA) uses a venous injection of contrast, and the timing to detect intracranial arterial filling is problematic. False positives have been reported with CTA, and its use in brain death determination has not been recommended by the AAN.³ This is not an ethical controversy as the authors would suggest in their dense discussion. Their evaluation was simply outside the standard of practice in the United States. There is nothing elusive about it.

Mayo Clinic (EFMW), Rochester, MN; and Yale University College of Medicine (DNG), New Haven, CT.

Disclosures: E. Wijndicks served as Editor-in-Chief for *Neurocritical Care* (2004–2012) and receives publishing royalties for books published by Oxford University Press. D. Greer receives publishing royalties for *Acute Ischemic Stroke: An Evidence-Based Approach* (Wiley and Sons, 2007); has served on speakers' bureaus for Boehringer-Ingelheim; and has received research support from Boehringer-Ingelheim.

James Zisfein, MD, Menachem Gold, MD: Story and Winter¹ report a patient who fulfilled clinical criteria for brain death but had a CT angiogram (CTA) that was interpreted as not confirming brain death because of preserved cerebral blood flow (CBF). We believe the CTA may have been misinterpreted. The provided images show contrast in the sylvian (M2) branches of the middle cerebral artery (MCA) but not in the cortical (M4) branches. This pattern occurs in brain death and does not indicate CBF. It is produced by stasis filling of proximal MCA branches.^{4–6} To confirm brain death by CTA, one must examine the cortical MCA branches, which are not affected by stasis filling.

Lincoln Medical Center, Bronx, NY.

Disclosures: The authors report no disclosures.

Authors Respond: Daryl Story, MD, Stephen Winter, MD: In an era where there is still wide variability in the process for determining brain death,⁷ we welcome the comments our report has produced.

We agree with Dr. Sethi that the concept and definition of brain death deserve discussion. It is indeed difficult to demonstrate lack of any cortical metabolic and electrical activity as he correctly states, yet this is necessary in today's practice.

In response to Drs. Zisfein and Gold, the CTA was interpreted by the radiologist who helped create our brain death policy, based on a 4-vessel protocol designed to reduce false negatives due to stasis filling.⁴ The slices displayed may not be fully representative.

Drs. Wijidicks and Greer raise additional important issues. Their criticism of our handling of the case, however, implies knowledge of specifics that could not be included in a brief report. The apnea test was performed by clinicians before the potential issue of the pharmacologic confounder was considered and debated at bedside. Furthermore, it could be argued that an attempt at excluding brain death by clinical exam would have obviated the need for any further testing. Decisions such as using CTA and not immediately proceeding with donation after cardiac death (DCD) were influenced by a grieving family that was ambivalent about consenting for organ donation in the first place. They wished for only minimal additional testing and were against the idea of DCD. We were doing our best to navigate these challenging real-life issues.

Stroke Center (DS) and Pulmonary and Critical Care Medicine (SW), Norwalk Hospital, CT; New York Medical College (DS), Valhalla; and Yale University (SW), New Haven, CT.

Disclosures: The authors report no disclosures.

1. Story D, Winter SM. An elusive brain death diagnosis: you can't get there from here. *Neurol Clin Pract* 2014;4:171–174.
2. Wijidicks EFM, Varelas PN, Gronseth GS, Greer DM. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2010;74:1911–1918.
3. Greer DM, Strozzyk D, Schwamm LH. False positive CT angiography in brain death. *Neurocrit Care* 2009;11:272–275.
4. Frampas ECT Angiography for brain death diagnosis. *AJNR* 2009;30:1566–1570.
5. Sawicki M, Bohatyrewicz R, Safranow K, et al. Dynamic evaluation of stasis filling phenomenon with computed tomography in diagnosis of brain death. *Neuroradiology* 2013;55:1061–1069.
6. Combes JC, Chomel A, Ricolfi F, d'Athis P, Freysz M. Reliability of computed tomographic angiography in the diagnosis of brain death. *Transplant Proc* 2007;39:16–20.
7. Shappell CN, Frank JI, Husari K, Sanchez M, Goldenberg F, Ardel A. Practice variability in brain death determination: a call to action. *Neurology* 2013;81:2009–2014.

Current controversies: Physicians vs Pharma

Nitin K. Sethi, MD: I read with great interest the debate between Dr. Corboy and Dr. Elliott about the relationship between physicians and Pharma.^{1,2} One lasting memory from my residency days is attending a Pharma-sponsored dinner (commonly known as a drug dinner among residents and fellows). A renowned epileptologist from an academic center of excellence in New York City was talking about Keppra (levetiracetam). As a resident I imbibed his words when he said that it was his drug of choice for patients with generalized epilepsy. The next week I heard the same epileptologist say the exact same thing, this time for Lamictal (lamotrigine), at another drug dinner sponsored by a different Pharma company. Residents and fellows in training have impressionable minds and their prescribing habits are more likely to be swayed by this type of targeted marketing than those of seasoned physicians. The authors also talk about more complete disclosures when it comes to research articles, other publications, and conference talks. While this is certainly a laudable goal, one must remember that disclosure does not imply the absence of bias, it only indicates a potential for bias. That

said, fraudulent and unethical interactions in the past between some physicians and Pharma should not result in radical policy changes that apply to all physicians and the entire pharmaceutical industry and are in the end detrimental to our patients. The pendulum has swung from lavish fully paid trips to the Bahamas to where accepting a pen is considered unethical and has to be reported. I hope somewhere between these 2 extremes there is a middle ground where common sense prevails and physicians and Pharma can work hand in hand to the benefit of our patients.

New York-Presbyterian Hospital.

Disclosures: N. Sethi serves as an Associate Editor for *The Eastern Journal of Medicine*.

Kevin Cwayna, MD: Thank you, Dr. Elliott, for stating the unstated. Pharma doesn't beat with a human heart and insurance companies haven't taken the Hippocratic oath.² Both are legally bound to shareholder profit as their singular drive. The moment we think otherwise, the health of our patients is in jeopardy. Patient health isn't the only sacrificial lamb of health businesses. Elliott alludes to another even more covert casualty—trust between the doctor and “customer.” If business can get “customers” to listen to them before doctors, why wouldn't they? Direct-to-consumer advertising, illegal in the European Union and most other parts of the world for this reason, is their wedge. It's a formidable medical authority perched to contradict us. I can see beyond the billions spent to humanize Pharma, but patients, “vulnerable and sometimes desperate,” may not. Don't take money from Pharma, but also guard your relationship with patients.

Urban Health Action, Long Beach, CA.

Disclosures: K. Cwayna serves as a consultant for Intellisight Partners, LLP.

Bryan Facca, RPh, PharmD: In his one-sided assault, Dr. Elliott describes Pharma, one of the most regulated industries in the world, as “not in the business of health care.” My question to Elliott's crusade: where will medicines come from? Pharma is highly regulated and held to a standard unlike any other business in this country. It is designed to create value not only for shareholders but also for society. Pharma employs some of the best scientists and methods to develop medicines and vaccines that make a meaningful difference to patients, health care providers, and payers. And let's not forget these medicines are approved by regulatory agencies. They are peer reviewed in journals and conferences by a group that is highly educated and knowledgeable on the subject: doctors! Medicines in development or on the market serve one primary purpose—to provide relief. Look at neurology: where are the cures for Parkinson disease, epilepsy, migraine, Alzheimer disease? A *joint effort* by physicians and Pharma is needed to continue research and develop medicines for unmet medical needs. Neither can go it alone. Pharma is comprised of science, creativity, and society. Molecules are synthesized, trials are designed, and results are socially integrated with physicians, payers, and patients. Pharma continues to refine this model as new information and understanding of biology, pharmacology, and pathology is gathered. Gone are the days of pens, logo paper, desk trinkets, and free lunches. All attendees are accounted for and publicly noted. An improved alliance is what is needed. Not a “say no” to money campaign.

Eisai, Alto, MI.

Disclosures: B. Facca is employed by Eisai as a Medical Science Liaison. NOTE: Views expressed here are those of the individual not his employer (Eisai).

Author Responds: John R. Corboy, MD, FAAN: I appreciate the letters and will respond for both myself and Dr. Elliott as he is unavailable at this time.

Dr. Cwayna has an opinion of Pharma quite similar to that of Dr. Elliott, thanking Dr. Elliott for “stating the unstated.” It is difficult to believe that any physician is not aware of significant negative statements about Pharma and its relationships with physicians over the last 20 years. The negative sentiments have been translated into self-regulatory behavioral changes within Pharma and massive amounts of time spent by physicians disclosing relationships, culminating soon in the complete disclosure of virtually any financial tie between Pharma and any physician,³ similar to the disclosures of Medicare spending released earlier this year. Indeed, there is substantial sentiment that the pendulum has swung way too far, with some suggesting there is no evidence that Pharma-MD relationships have harmed patients,⁴ and, if enacted, the calls to limit interactions with Pharma may well lead to negative outcomes for our patients. The last line from Dr. Cwayna illustrates 2 important concepts in this debate. The first is that it is not so simple to say “Don’t take money from Pharma.” What does this mean? I hope he is not suggesting that receiving money from Pharma to have an article “ghostwritten” or giving a canned marketing talk using content developed exclusively by, and carrying the logo of, Pharma is equivalent to running a phase III trial of a medication that may change the lives of millions of people? I don’t view these activities as similar functionally or morally. The second is that he raises an appropriate concern about intrusions by Pharma into the patient-physician relationship, manifested by electronic or face-to-face direct-to-patient marketing techniques. While I share his concern about these marketing behaviors, the time when the physician was the only (seemingly) credible authority in health matters is long past. Free access to the Internet poses at least as large a problem with dissemination of dubious and self-serving speech as Pharma. At least the US Food and Drug Administration regulates Pharma in some manner.

Dr. Facca, on the other hand, offers a much more optimistic—some might say rose-colored—view of Pharma, and outlines the positive roles of Pharma in our society. While not discussing any of the negative aspects as highlighted by Elliott and Cwayna, he correctly makes the point that we all need medications, that Pharma is regulated by multiple agencies, and that the publications they generate are reviewed by multiple scholars, including physicians such as ourselves; i.e., there are a number of appropriate societal controls in place to monitor their behavior. Of course, regulation does not alter all behavior, only that which comes to light and is found to be seriously unacceptable. And while I am uncertain as to what Pharma has contributed in campaign dollars specifically, the “free speech” of massive campaign donations has been used in attempts to defeat those who call for more business regulation. I suspect that more than a few physicians reading his description that Pharma is “held to a standard unlike any other business” are just shaking their heads.

Perhaps Dr. Sethi strikes the appropriate balance that we need to find a way to coexist and do the right thing, together, and not throw out the baby with the bathwater. In his description of the physician expert speaking out of both sides of his mouth, he alludes to the choices we as physicians can make when interacting with Pharma. Either we can work to further the ends of Pharma, enriching ourselves by accepting monies to that end, or we can find the ethical and moral plateaus that allow us to work *with* Pharma while working *for* our patients. The unique aspect of our existence as physicians is that we are both a business and medical professionals who cradle in our hands the fate of vulnerable patients. As a result, we are held, correctly, to a higher standard than someone who sells pencils. It is in this context that we must not only police ourselves and disclose relationships but also accept that the rest of society and, most importantly, our individual patients, have instilled in us a level of trust that is virtually unmatched. We cannot betray that trust. If we remember that and act with our patients’ best interests at heart, I think we can navigate this minefield. The relationships will be constantly changing as we evolve in the future, and vigilance will need to be maintained and enhanced as we go forward.

University of Colorado School of Medicine, Rocky Mountain Multiple Sclerosis Center at AMC, Aurora, CO.

Disclosures: J. Corboy served as a Section Editor for *Neurology Today* and serves as editor of *Neurology: Clinical Practice*; serves on the speakers’ bureau for ProCE; receives/received research support from Genentech, Novartis,

Biogen Idec, Teva, Eli Lilly, Orasi Medical, NIH, Juvenile Diabetes Research Foundation, and National MS Society; and has participated in medico-legal cases.

1. Corboy JR. The relationship between physicians and Pharma: playing the devil's advocate. *Neurol Clin Pract* 2014;4:161–163.
2. Elliott C. Relationships between physicians and Pharma: why physicians should not accept money from the pharmaceutical industry. *Neurol Clin Pract* 2014;4:164–167.
3. Available at: <http://www.cms.gov/Regulations-and-Guidance/Legislation/National-Physician-Payment-Transparency-Program/index.html>. Accessed June 21, 2014.
4. Barton D, Stossel T, Stell L. After 20 years, industry critics bury skeptics, despite empirical vacuum. *Int J Clin Pract* 2014;68:666–673.

Share Your Knowledge

Neurology® Clinical Practice encourages readers to share their insights, expertise, and experiences.

- How are you employing drugs and devices in your field?
- What ethical challenges do you face?
- Do you have a case report that is illustrative of a clinical challenge?
- What challenges have you faced or successes have you enjoyed in bringing greater efficiency to your practice?

If you are interested in delivering a high-quality, peer-reviewed message to your colleagues in practice, submit your paper **online**.

Neurology® Clinical Practice

An elusive brain death diagnosis: You can't get there from here

Nitin K. Sethi, Eelco F. M. Wijdicks, James Zisfein, et al.

Neurol Clin Pract 2014;4;272-273

DOI 10.1212/CPJ.0000000000000052

This information is current as of August 18, 2014

Updated Information & Services	including high resolution figures, can be found at: http://cp.neurology.org/content/4/4/272.full.html
References	This article cites 7 articles, 2 of which you can access for free at: http://cp.neurology.org/content/4/4/272.full.html##ref-list-1
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://cp.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://cp.neurology.org/misc/addir.xhtml#reprintsus

Neurol Clin Pract is an official journal of the American Academy of Neurology. Published continuously since 2011, it is now a bimonthly with 6 issues per year. Copyright © 2014 American Academy of Neurology. All rights reserved. Print ISSN: 2163-0402. Online ISSN: 2163-0933.