

# The Nerve! Readers Speak

## Reader Response: Practice Current: When do you order ancillary tests to determine brain death?

Calixto Machado, and Mario Estévez (Havana, Cuba)

*Neurology: Clinical Practice* October 2018 vol. 8 no. 5 364 doi:10.1212/CPJ.0000000000000537

We recently reported a case (case 3 in our article)<sup>1</sup> contributing to the discussion of using ancillary tests in brain death.<sup>2</sup> This case showed brain death clinical features leading to a death certification. We studied the case 9 months later.<sup>1</sup> We found preservation of intracranial structures, with a huge lesion at the brainstem.<sup>1</sup> Conceptually, brain death is characterized by absence of cerebral blood flow.<sup>3</sup> Conservancy of brain structures rejects brain death diagnosis.<sup>1,3</sup> EEG signal was found in this case. EEG signal may persist in posterior fossa catastrophes.<sup>2</sup> Using heart rate variability (HRV) methodology, we found preservation of all HRV bands, contrary to reports in brain death.<sup>4</sup> This case also showed autonomic reactivity to “mother talks” stimulation. This is a demonstration of autonomic CNS activity preservation.<sup>1</sup> Our patient showed brain death clinical features, but the use of ancillary tests denied this diagnosis. We claimed that this is a new state, not previously classified, of a disorder of consciousness.<sup>1</sup> Is there a diagnosis of any disease in which a confirmatory test (blood test, imaging) is not used, considering that pitfalls in clinical examination can occur? Brain death determination is the most challenging diagnosis for a physician. Why not use a confirmatory test?<sup>1,5</sup>

1. Machado C, DeFina PA, Estévez M, et al. A reason for care in the clinical evaluation of function on the spectrum of consciousness. *J Funct Neurol Rehabil Ergon* 2017;7:43–53.
2. Robbins NM, Bernat JL. Practice Current: when do you order ancillary tests to determine brain death? *Neurol Clin Pract* 2018;8:266–274.
3. Bernat JL. On irreversibility as a prerequisite for brain death determination. *Adv Exp Med Biol* 2004;550:161–167.
4. Su CF, Kuo TB, Kuo JS, Lai HY, Chen HI. Sympathetic and parasympathetic activities evaluated by heart-rate variability in head injury of various severities. *Clin Neurophysiol* 2005;116:1273–1279.
5. Machado C, Estévez M, Portela L. Improving uniformity in brain death determination policies over time. *Neurology* 2017;88:562–568.

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## Author Response: Practice Current: When do you order ancillary tests to determine brain death?

Nathaniel M. Robbins, and James L. Bernat (Lebanon, NH)

*Neurology: Clinical Practice* October 2018 vol. 8 no. 5 364 doi:10.1212/CPJ.0000000000000539

We thank Machado and Estévez for their comment on our article.<sup>1</sup> We agree that ancillary tests clearly have a role in the diagnosis of brain death, but the issue is complex, as the 3 experts pointed out in their commentaries. We also agree that the case 3 they cited in their article (Jahi McMath) is an important case that requires further study to interpret correctly.<sup>2</sup>

1. Robbins NM, Bernat JL. Practice Current: when do you order ancillary tests to determine brain death? *Neurol Clin Pract* 2018;8:266–274.
2. Machado C, DeFina PA, Estévez M, et al. A reason for care in the clinical evaluation of function on the spectrum of consciousness. *J Funct Neurol Rehabil Ergon* 2017;7:43–53.

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## Reader Response: FACETS of health disparities in epilepsy surgery and gaps that need to be addressed

Nitin K. Sethi, New York, NY

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I read with interest the commentary by Nathan and Gutierrez<sup>1</sup> on the causes of health disparities in epilepsy surgery and how these can be addressed. Many patients initially resist epilepsy surgery for the simple reason that it is surgery. I have patients who are good candidates for resective epilepsy surgery and in spite of my best efforts they have steadfastly resisted the surgical option. Maintaining continuity of care over years with reassurance and gentle persuasion, I have succeeded in guiding some of these patients towards a surgical option with gratifying results. It is important for us physicians to remember that medicine is a field which requires dedication and perseverance.

1. Nathan CL, Gutierrez C. FACETS of health disparities in epilepsy surgery and gaps that need to be addressed. *Neurol Clin Pract* 2018;8:340–345.

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## Author Response: FACETS of health disparities in epilepsy surgery and gaps that need to be addressed

Camilo A. Gutierrez, Baltimore, MD

*Neurology: Clinical Practice* October 2018 vol. 8 no. 5 365 doi:10.1212/CPJ.0000000000000538

We appreciate the comment by Dr. Sethi highlighting the reluctance of some patients to obtain surgery. The disparity seen in epilepsy surgery utilized by African American and Hispanic patients compared to non-Hispanic white patients suggests that specific factors disproportionately affect these groups. We proposed FACETS as a framework to begin to understand and study these potential factors.<sup>1</sup> We agree that dedication, perseverance, and continuity of care are valuable interventions that may drive epilepsy surgery. We are also concerned that delay in epilepsy surgery may lead to preventable morbidity and mortality.<sup>2</sup> We should actively work at breaking down the barriers that cause delay and underutilization of epilepsy surgery for all patients with drug-resistant epilepsy.

1. Nathan CL, Gutierrez C. FACETS of health disparities in epilepsy surgery and gaps that need to be addressed. *Neurol Clin Pract* 2018;8:340–345.
2. Choi H, Sell RL, Lenert L, et al. Epilepsy surgery for pharmacoresistant temporal lobe epilepsy: a decision analysis. *JAMA* 2008;300:2497–2505.

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## Reader Response: Exercise for cognitive brain health in aging: A systematic review for an evaluation of dose

Matthew P. Pase, Melbourne, Australia

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One of the 3 aims of the review by Gomes-Osman et al.<sup>1</sup> was to identify consistent patterns of exercise on domains of cognition. The authors are to be commended for such an ambitious task. The creation of cognitive composite scores requires careful attention to eliminate bias

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and to ensure that outcomes are theoretically valid and meaningful. In their study, the authors grouped neuropsychological tests from the reviewed studies into 5 outcomes: executive function, processing speed/attention, global cognition, working memory, and visuospatial processing/memory. However, the validity of these broad cognitive domains is uncertain; no cognitive model or theory was cited as a rationale for their creation, their definition was not described, and no data were provided to show which neuropsychological tests were included in each domain. Consequently, the patterns of cognitive improvement with exercise remain uncertain. The large number of neuropsychological tests used across studies poses unique challenges for systematic reviews. However, extensive factor analytic work has provided evidence-based “cognitive maps” akin to the periodic table of elements.<sup>2-4</sup> This framework can be used to guide the handling and analysis of cognitive outcomes in reviews, helping to eliminate bias and ensuring that cognitive domains are theoretically valid and meaningful.<sup>5</sup>

1. Gomes-Osman J, Cabral DF, Morris TP, et al. Exercise for cognitive brain health in aging: a systematic review for an evaluation of dose. *Neurol Clin Pract* 2018;8:257–265.
2. Carroll JB. *Human Cognitive Abilities: A Survey of Factor Analytic Studies*. New York: Cambridge University Press; 1993.
3. Carroll JB. The three-stratum theory of cognitive abilities. In: Flanagan DP, Harrison PL, eds. *Contemporary Intellectual Assessment: Theories, Tests and Issues*, 3rd ed. New York: Guilford Press; 2012.
4. McGrew KS. The Cattell-Horn Carroll theory of cognitive abilities: past, present and future. In: Flanagan DP, Harrison PL, eds. *Contemporary Intellectual Assessment: Theories, Tests and Issues*, 2nd ed. New York: The Guilford Press; 2005.
5. Pase MP, Stough C. An evidence based method for examining and reporting cognitive processes in nutrition research. *Nutr Res Rev* 2014;27:232–241.

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## Author Response: Exercise for cognitive brain health in aging: A systematic review for an evaluation of dose

Timothy P. Morris (Boston, MA), Joyce Gomes-Osman (Miami, FL), and Alvaro Pascual-Leone (Boston, MA)  
*Neurology: Clinical Practice* October 2018 vol. 8 no. 5 366–368 doi:10.1212/CPJ.0000000000000532

We thank Dr. Pase for his comments regarding our systematic review.<sup>1</sup> We share Dr. Pase’s concern that a very large number of different cognitive tasks have been used in past studies on the effects of exercise, which poses substantial challenges to systematic reviews. Furthermore, as pointedly stated by Colcombe and Kramer<sup>2</sup> in a review of exercise and cognitive function, considerable overlap in cognitive constructs exists. We appreciate Dr. Pase’s suggestion of considering the framework offered by cognitive maps and agree with their promise and value. Having the ability to prescribe the correct exercise dose for a specific cognitive domain would provide a wonderful tool for clinicians that would push the field beyond theoretical status into an established, evidence-based treatment.

Providing an exhaustive and definitive classification of cognitive domains modulated by exercise was beyond the scope of our review. The primary objective was to analyze consistent patterns in the measures of exercise for an evaluation of dose as a first step towards evidence-based prescriptions of exercise. Consequently, when assessing the consistent effects of exercise on different cognitive domains, we felt that it was most appropriate to align the methods with previously published classifications of cognitive domains within the exercise literature.<sup>2,3</sup> As stated in the methods, a board-certified, PhD-trained clinical neuropsychologist oversaw the classifications. We agree that a list of cognitive tasks that met each cognitive domain (similar to that presented in Smith et al.<sup>3</sup>) is helpful (table).

**Table** Classification of neuropsychological tests by cognitive domain

| Processing speed/attention            | Executive functions                      | Working memory                      | Visuospatial/memory                      | Global cognition                             |
|---------------------------------------|--|-------------------------------------|--|--|
| Finger tapping                        | Categorical fluency (animal naming)      | Digit span backward                 | ADAS word list recall                    | ADAS-cog                                     |
| Digit Symbol Substitution Test        | Go/no-go test                            | N-back task                         | Auditory Verbal Learning Test            | Neurobehavioral cognitive status examination |
| Attentive matrices                    | Raven's progressive matrices             | WAIS letter-number sequencing       | Benton Visual Retention Test             | Mini-Mental State Examination                |
| Ruff 2 & 7 test (letters)             | RIPA organization                        | Letter search                       | RAVLT short                              | 5-Cog  |
| Age concentration test A and B        | RIPA problem-solving                     | Memory for health information       | RAVLT delay/retention                    | Dementia Rating Scale                        |
| Simple/choice time                    | RIPA abstract reasoning                  | Digit span forward                  | RAVLT total                              | Clinical Dementia Rating                     |
| Attention task                        | Digits (Ruff 2 & 7 test)                 | SOPT                                | RBMT faces                               | Neuropsychological test battery              |
| Speed of movement                     | Drawing Copy Test                        | Spatial working memory task         | Boston Naming Test                       | Rapid Evaluation of Cognitive Functions Test |
| Stroop color                          | Motor control (CANTAB)                   | Executive control task              | RBMT pictures                            | Rey-Osterrieth complex figure                |
| Stroop word                           | Set-shifting ability                     | Letter-number sequencing (WAIS III) | Pattern recognition memory test (CANTAB) | CAMCOG                                       |
| Task-switching RT                     | Stroop color/word or interference        | Running memory span task            | RIPA auditory processing                 |  |
| Trail-making test part A              | Trail-making test part B                 | Spatial working memory (CANTAB)     | RIPA immediate memory                    |  |
| Digit vigilance                       | Useful field of view                     | Cooking breakfast task              | RIPA recent memory                       |  |
| Digit span forward                    | Subtraction task (dual)                  |                                     | Visual and verbal memory test            |  |
| Symbol search test                    | WAIS III (matrices and similarities)     |                                     | Selective Reminding Test                 |  |
| Digit Symbol Substitution Test        | Wisconsin Card-Sorting Task              |                                     | VLMT delayed recall                      |  |
| A Quick Test of Cognitive Speed (AQT) | Randt memory test story recall           |                                     | WMS logical memory, immediate            |  |
| Direction headings                    | Frontal Assessment Battery               |                                     | WMS logical memory, delayed              |  |
| Bell cancellation test                | COWAT                                    |                                     | WMS verbal paired associates             |  |
| Number comparison test                | CVFT                                     |                                     | Hopkins verbal memory                    |  |
| Plate tapping test                    | Color trails test                        |                                     | Clock-drawing test                       |  |
| Digit symbol coding                   | Eriksen flanker test                     |                                     | Story recall                             |  |
| Symbol Digit Modalities Test          | Random number generation task            |                                     | List learning (ADAS-cog)                 |  |
| Wisconsin Card-Sorting Test           | Letter sets test                         |                                     | Useful field of view test                |  |
| Useful field of view task             | Congruent and incongruent reaction times |                                     | Short story module (Randt memory test)   |  |

Continued

Author disclosures are available upon request (ncpjjournal@neurology.org)

**Table** Classification of neuropsychological tests by cognitive domain (continued)

| Processing speed/attention                   | Executive functions                 | Working memory | Visuospatial/memory                    | Global cognition |
|--|-------------------------------------|----------------|--|------------------|
| Stanford Sleepiness Scale                    | Matrix reasoning test               |                | Free and Cued Selective Reminding Test |                  |
| Rapid visual information processing (CANTAB) | Trail-making test part A            |                | Word comparison                        |                  |
| Digit span backward                          | Verbal fluency (category or letter) |                | Directional headings test              |                  |
| Time-sharing                                 | Local switch cost                   |                | Virtual week task                      |                  |
| D-cat  | Category fluency (ADST)             |                | First and second names                 |                  |
| Letter-digit                                 | Turning point index                 |                | Verbal learning and memory test        |                  |
|  | The Adjacency Test                  |                | Cooking breakfast task                 |                  |
|  | Runs index                          |                | Benton Visual Retention Test           |                  |
|  | Dots estimation                     |                | Complex Figure Test                    |                  |
|  |                                     |                | VCP test                               |                  |
|  |                                     |                | Delayed recall (WMS-R)                 |                  |
|  |                                     |                | Finger-movement tracking test          |                  |
|  |                                     |                | Mental rotation                        |                  |
|  |                                     |                | Visual paired associates               |                  |
|  |                                     |                | Letter fluency                         |                  |
|  |                                     |                | Drawing copy test                      |                  |
|  |                                     |                | Chinese verbal learning                |                  |
|  |                                     |                | Brief Visuospatial Memory Test         |                  |
|  |                                     |                | Word list fluency test                 |                  |

Abbreviations: ADAS = Alzheimer's Disease Assessment Scale; ADAS-cog = Alzheimer's Disease Assessment Scale cognitive subscale; ADST = Amsterdam Dementia Screening Test; CAMCOG=Cambridge Cognition Examination;CANTAB = Cambridge Neuropsychological Test Automated Battery; COWAT = Controlled Oral Word Association Task; CVFT = Category Verbal Fluency Test; RAVLT = Rey Auditory Verbal Learning Test; RBMT = Rivermead Behavioral Memory Test; RIPA = Ross Information Processing Assessment; RT = reaction time; SOPT = self-ordered pointing test; VCP = Visuospatial Cognitive Performance; VLMT = Verbal Learning and Memory Test; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale.

- Gomes-Osman J, Cabral DF, Morris TP, et al. Exercise for cognitive brain health in aging: a systematic review for an evaluation of dose. *Neurol Clin Pract* 2018;8:257–265.
- Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci* 2003;14:125–130.
- Smith PJ, Blumenthal JA, Hoffman BM. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med* 2010;72:239.

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## Reader Response: Ask a neurologist: What primary care providers ask, and reducing referrals through eConsults

Roger R. Hesselbrock, Wright-Patterson AFB, OH

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I read with interest the article by Bradi et al.<sup>1</sup> and the editorial by Nuwer and Corboy<sup>2</sup> about the eConsults program. I am part of the military teleconsultation group cited in the editorial,<sup>3</sup> and as of March 2018 I have provided input to over 360 requests. Similar to the authors' experience, most requests involved management guidance, particularly whether the patient would be able to remain in place or would need transfer for further evaluation. Besides this program, I routinely receive e-consult requests on aeromedical issues from Air Force providers worldwide. These requests generally do not involve acute management, but cover questions about the diagnosis, suitability for return to flying, recommended evaluation, recommended observation period, and medical standards. In addition to answering the referring provider's questions, teaching points and references were included where applicable. I am fortunate to have a closed, secure messaging platform, a system-wide electronic medical record that can capture any additional documentation, and do not have concerns on licensing portability, which alleviate some of the concerns Bradi et al. address with civilian applications. I concur with Bradi et al. that provider-to-provider electronic consultations are a powerful and effective management tool.

1. Bradi AC, Sitwell L, Liddy C, Afkham A, Keely E. Ask a neurologist: what primary care providers ask, and reducing referrals through eConsults. *Neurol Clin Pract* 2018;8:186–191.
2. Nuwer MR, Corboy JR. Curbside consults join the telemedicine era. *Neurol Clin Pract* 2018;8:177–178.
3. Yurkiewicz IR, Lappan CM, Neely ET, et al. Outcomes from a US military neurology and traumatic brain injury telemedicine program. *Neurology* 2012;79:1237–1243.

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## Author Response: Ask a neurologist: What primary care providers ask, and reducing referrals through eConsults

Ana C. Bradi, Ottawa, Canada

*Neurology: Clinical Practice* October 2018 vol. 8 no. 5 369–370 doi:10.1212/CPJ.0000000000000536

We are pleased to see that our article<sup>1</sup> has sparked discussion within the neurology community and introduced the premise that patient care can be improved with fast and secure communication between primary care providers (PCPs) and specialists.

We hope to clarify some points brought up in the accompanying editorial.<sup>2</sup> In Ontario, eConsults are a recognized means for providing medical expertise and therefore there is a specific fee associated with providing this service. Once a neurologist or any other specialist receives and reads an eConsult, it is up to his or her judgement whether the questions can be answered in this format. If he or she is uncomfortable giving advice without assessing the patient, he or she is able to ask the PCP to send a formal consult request. Similarly, if more information is needed and can be requested from the PCP, this can also be done. Even in these circumstances, there is an opportunity to suggest testing that can help determine a clinical opinion faster once the patient is formally assessed. A formal consult can be requested if management decisions hinge on reviewing MRI and EEG raw images or waveforms. As mentioned in our article, a formal consult was requested in 3% of cases where PCPs did not initially think it was required.

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Author disclosures are available upon request (ncpjjournal@neurology.org)

Based on our review, eConsults are mostly being requested in situations where the patient is considered to be at low risk. In many cases, the need for formal assessment is in question or reassurance is desired about an intended workup or management plan. There have not been any issues with litigation to date stemming from using this system. Moving forward, it will be interesting to assess how this system has affected patient outcomes.

1. Bradi AC, Sitwell L, Liddy C, Afkham A, Keely E. Ask a neurologist: what primary care providers ask, and reducing referrals through eConsults. *Neurol Clin Pract* 2018;8:186–191.
2. Nuwer MR, Corboy JR. Editorial: curbside consults join the telemedicine era. *Neurol Clin Pract* 2018;8:177–178.

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## Reader Response: Clinical factors associated with Guillain-Barré syndrome following surgery

Nathaniel M. Robbins, MD, Lebanon, NH

*Neurology: Clinical Practice* October 2018 vol. 8 no. 5 370 doi:10.1212/CPJ.0000000000000534

I read with interest the article by Hocker et al.<sup>1</sup> I took care of a 45-year-old man several years ago with neurotropic squamous cell carcinoma of the oropharynx (T2N0M0). His brother and paternal uncle had testicular cancer, and his mother had breast cancer. Three months after his initial resection, he developed neuropathic pain of the tongue, and MRI showed tumor recurrence. Two weeks later, he developed classic Miller-Fisher syndrome with mild ophthalmoparesis, ataxia, areflexia, elevated CSF protein, and an elevated anti-Gq1b. He was treated with IV immunoglobulin and did well. Two weeks later, he underwent repeat surgery. In the days following this, he developed neuropathic pain in the right shoulder that persisted for a month and was followed by atrophy and weakness in several right arm muscles. Clinical and electrodiagnostic testing confirmed a diagnosis of brachial neuritis.

As the authors pointed out, surgeries are common, and even tumor surgeries are not infrequent. In contrast, postsurgical immune-mediated neuropathies are rare, and even more rarely paraneoplastic. I would hypothesize that both characteristics of the tumor and genetic factors matter: Was there any preponderance for neurotropism in the tumors in this series? Did cancer run in these patients' families?

1. Hocker S, Nagarajan E, Rubin M, Wijdicks EFM. Clinical factors associated with Guillain-Barré syndrome following surgery. *Neurol Clin Pract* 2018;8:201–206.

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**Editor's Note:** The authors of the article were offered the opportunity to respond but declined as they were asked by the reviewers not to postulate as to the mechanism.

## Reader Response: Rabies encephalitis presenting with new-onset refractory status epilepticus (NORSE)

Alan C. Jackson, and Marc R. Del Bigio (Winnipeg, Canada)

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We read the recent case report by Villamar et al.<sup>1</sup> and have concerns about the conclusion that the patient died of rabies. First, it would be useful to know when the case occurred and whether there was any history of an animal exposure. This is basic historical information that

should be sought in a case of suspected rabies and could be obtained postmortem if the diagnosis was not considered during life. Second, the initial 1-month history of personality change and declining academic performance and the 2-week gap between the initial seizure and the status epilepticus are incompatible with rabies encephalitis, which is characterized by rapid progressive neurologic deterioration once neurologic symptoms and signs are present.<sup>2</sup> Third, the illustrated eosinophilic body associated with a neuron is not indisputably a Negri body. Its location could be paraneuronal rather than intracytoplasmic. Negri bodies are intraneuronal cytoplasmic inclusion bodies that contain rabies virus RNA and proteins.<sup>3</sup> Negri body–like inclusions, some consisting of endoplasmic reticulum distended by proteinaceous material, have been described in other conditions.<sup>4–6</sup> Fourth, detailed studies of human cases showed that all neurons with Negri bodies also expressed detectable rabies virus antigen.<sup>7,8</sup> Rabies virus antigens are easily detected using immunohistochemical methods in formalin-fixed paraffin-embedded tissues using polyclonal or monoclonal anti-rabies virus antibodies.<sup>3</sup> Failure to detect rabies virus antigens in a fatal case would need to be explained by improper tissue preparation involving excessive fixation. The report of a positive in situ reverse transcription PCR (RT-PCR) result with no supporting images and a detailed description of the anatomical localization is inadequate. There was no mention made of conventional RT-PCR results for rabies virus RNA.<sup>9</sup> There was no description of positive or negative controls for the immunohistochemistry and in situ RT-PCR studies. Could other standard cellular (e.g., neuronal) antigens be detected in the tissues? With the available information reported, the evidence that the patient died of rabies is unconvincing.

1. Villamar MF, Smith JH, Wilson D, Smith VD. Rabies encephalitis presenting with new-onset refractory status epilepticus (NORSE). *Neurol Clin Pract* 2017;7:421–424.
2. Jackson AC. Human disease. In: Jackson AC, ed. *Rabies: Scientific Basis of the Disease and its Management*, 3rd ed. Oxford: Elsevier Academic Press; 2013:269–298.
3. Rossiter JP, Jackson AC. Pathology. In: Jackson AC, ed. *Rabies: Scientific Basis of the Disease and its Management*, 3rd ed. Oxford: Elsevier Academic Press; 2013:351–386.
4. Zhrebitskiy V, Del Bigio MR. Eosinophilic intracytoplasmic inclusions in Purkinje neurons of children. *Neuropathology* 2009;29:9–12.
5. Derakhshan I. Is the Negri body specific for rabies? A light and electron microscopical study. *Arch Neurol* 1975;32:75–79.
6. Szlachta HL, Habel RE. Inclusions resembling Negri bodies in the brains of nonrabid cats. *Vet Cornell* 1953;43:207–212.
7. Jackson AC, Ye H, Ridaura-Sanz C, Lopez-Corella E. Quantitative study of the infection in brain neurons in human rabies. *J Med Virol* 2001;65:614–618.
8. Nuovo GJ, DeFaria DL, Chanona-Vilchi JG, Zhang Y. Molecular detection of rabies encephalitis and correlation with cytokine expression. *Mod Pathol* 2005;18:62–67.
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## Author Response: Rabies encephalitis presenting with new-onset refractory status epilepticus (NORSE)

Jonathan H. Smith (Phoenix, AZ), Gerard J. Nuovo (Columbus, OH), and Mauricio F. Villamar (Boston, MA)  
*Neurology: Clinical Practice* October 2018 vol. 8 no. 5 371–372 doi:10.1212/CPJ.0000000000000543

We thank Drs. Jackson and Del Bigio for their comments on our case report.<sup>1</sup> The authors argue that there were insufficient data to support a diagnosis of rabies encephalitis, but do not offer an alternative, more cohesive explanation for the reported findings. The history of a fulminant and fatal course of new-onset refractory status epilepticus would be consistent, in our viewpoint, with what they believe does not qualify for a “rapid progressive neurologic deterioration.” It is certainly possible that the nonspecific symptoms of personality change and declining academics in the preceding month were unrelated.

This case was diagnosed in 2003 in a patient from rural northeastern Kentucky who resided in an area where numerous caves are found. While no evidence of exposure to a rabid animal was



confirmed, this is consistent with epidemiologic data showing that, in the United States, up to 80% of indigenous cases of rabies are cryptic.<sup>2</sup>

The identified inclusions in our case were intracytoplasmic and highly consistent with Negri bodies. Drs. Jackson and Del Bigio correctly point out that inclusions resembling Negri bodies have been observed in other disorders.<sup>3,4</sup> However, none of the previously reported conditions associated with Negri-like bodies, such as developmental disorders and Reye syndrome, would account for the clinical presentation observed in this case.

With regards to the *in situ* reverse transcription PCR (RT-PCR), it is important to stress that internal negative and positive controls are built into every experiment and, indeed, every slide. This is in contrast to external controls, which include the use of “irrelevant” primers (in place of the rabies primers, negative control) and omission of the DNase step (positive control),<sup>5</sup> which were done in this case.

By internal controls, we mean the distribution of the signal among the different cell types as they relate to what is well-documented regarding rabies infection of the CNS. The signal for rabies *in situ* RT-PCR was found in cells with the cytologic features of neurons. It was not found in cells with the cytologic features of endothelial cells, oligodendroglial cells, or astrocytes. Further, the cells with the intracytoplasmic inclusions had the cytologic features of neurons and it was these cells that showed a signal with *in situ* RT-PCR for rabies. This is strong evidence for the specificity of the reaction.

Thus, in this unusual case, the clinical, pathologic, and molecular evaluation was most consistent with a diagnosis of rabies encephalitis.

1. Villamar MF, Smith JH, Wilson D, Smith VD. Rabies encephalitis presenting with new-onset refractory status epilepticus (NORSE). *Neurol Clin Pract* 2017;7:421–424.
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3. Zherebitskiy V, Del Bigio MR. Eosinophilic intracytoplasmic inclusions in Purkinje neurons of children. *Neuropathology* 2009;29:9–12.
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5. Nuovo GJ, DeFaria DL, Chanona-Vilchi JG, Zhang Y. Molecular detection of rabies encephalitis and correlation with cytokine expression. *Mod Pathol* 2005;18:62–67.

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# Neurology® Clinical Practice

**Reader Response: Exercise for cognitive brain health in aging: A systematic review for an evaluation of dose**

Matthew P. Pase

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