Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Generalized polyspike train: An EEG biomarker of drug-resistant idiopathic generalized epilepsy

In the article "Generalized polyspike train: An EEG biomarker of drug-resistant idiopathic generalized epilepsy", Sun et al. reported the results of a case-control study with a discovery cohort and a replication cohort independently assessed at 2 centers, in which patients with idiopathic generalized epilepsy and generalized spike-wave discharges on EEG were classified as drug resistant or drug responsive. They found that the proportion of patients with generalized polyspike train (burst of generalized rhythmic spikes lasting less than 1 second) during sleep was higher in the drug-resistant group in both cohorts. In response, Drs. Rubboli and Gardella report similar EEG findings in a cohort of 12 adult patients with drug-resistant typical absences. Noting that these patients did not show any muscular activation concomitant with the generalized polyspike trains, they suggest that these trains have different pathophysiologic origins than the generalized paroxysmal fast activity seen in Lennox-Gastaut syndrome, but may share a similar dysfunction in γ-aminobutyric acid–mediated cortical inhibition as that seen with the polyspike discharges in juvenile myoclonic epilepsy.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
Neurology® 2019;93:562. doi:10.1212/WNL.0000000000008140

Reader response: Generalized polyspike train: An EEG biomarker of drug-resistant idiopathic generalized epilepsy

Guido Rubboli (Copenhagen and Dianalund, Denmark) and Elena Gardella (Dianalund, Denmark)
Neurology® 2019;93:562–563. doi:10.1212/WNL.0000000000008141

We read with interest the article by Sun et al.[1] We agree that generalized polyspike trains (GPTs) during sleep can represent an EEG feature of drug resistance in idiopathic generalized epilepsies (IGEs). We reported strikingly similar EEG findings in 12 adult patients with drug-resistant typical absences as prominent seizure type.[2] In our cohort, GPTs lasted <1 second and occurred during non-REM sleep in 66.6% of subjects, a proportion similar to the 73.7% reported in the discovery cohort by Sun et al.[1] In our study,[2] polygraphic recording, including EMG monitoring, did not show any muscular activation or other changes concomitant with GPTs, lending support to the hypothesis that GPTs in IGE and generalized paroxysmal fast activity in Lennox-Gastaut syndrome, the EEG hallmark of tonic seizures, might result from different pathophysiologic mechanisms. Polyspike frequency in GPTs falls within the range of the frequency of the polyspike discharge (i.e., 16–27 Hz) of the polyspike-wave complex of juvenile myoclonus epilepsy,[3] a form of IGE in which a deficit of γ-aminobutyric acid–mediated cortical inhibition has been shown.[4] This may suggest that a similar dysfunction, possibly genetically determined,[5] might influence the generation of polyspike EEG activities also in other forms of IGE.[1]

1. Sun Y, Seneviratne U, Perucca P, et al. Generalized polyspike train: an EEG biomarker of drug-resistant idiopathic generalized epilepsy. Neurology 2018;91:e1822–e1830.

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

2. Michelucci R, Rubboli G, Passarelli D, et al. Electroclinical features of idiopathic generalised epilepsy with persisting absences in adult life. J Neurol Neurosurg Psychiatry 1996;61:471–477.
3. Serafini A, Rubboli G, Gigli GL, Koutroumanidis M, Gelisse P. Neurophysiology of juvenile myoclonic epilepsy. Epilepsy Behav 2013; 28(suppl 1):S30–S39.
4. Manganotti P, Bongiovanni LG, Zanette G, Fiaschi A. Early and late intracortical inhibition in juvenile myoclonic epilepsy. Epilepsia 2000;41:1129–1138.
5. Johannesen K, Marini C, Pfeffer S, et al. Phenotypic spectrum of GABRA1: from generalized epilepsies to severe epileptic encephalopathies. Neurology 2016;87:1140–1151.

Editors' note: Depressed TSH level as a predictor of poststroke fatigue in patients with acute ischemic stroke

In the article "Depressed TSH level as a predictor of poststroke fatigue in patients with acute ischemic stroke", Wang et al. found that serum levels of thyroid stimulating hormone were inversely associated with risk and severity of poststroke fatigue (PSF) in 704 consecutive patients with ischemic stroke, suggesting that neuroendocrine responses could have a role in PSF. In response, Dr. Bunevicius notes that thyroid hormone concentrations fluctuate in the acute phase of stroke, making it difficult to estimate whether single-point thyroid-related measurements reflect prior or new hormonal balance or an acute response, and provides examples of medications and interventions that may interfere with thyroid gland functioning in the acute stroke setting. Dr. Bunevicius also suggests examining the relationship of the triiodothyronine to thyroxin ratio and PFS severity. The authors did not respond to these comments.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
Neurology® 2019;93:563. doi:10.1212/WNL.0000000000008139

Reader response: Depressed TSH level as a predictor of poststroke fatigue in patients with acute ischemic stroke

Adomas Bunevicius (Boston)
Neurology® 2019;93:563–564. doi:10.1212/WNL.0000000000008142

Wang et al.[1] reported that in patients with acute ischemic stroke, lower concentrations of thyroid-stimulating hormone were associated with greater fatigue symptom severity in acute phase and at follow-up. The article contributes to the growing body of literature underscoring the importance of thyroid axis function for clinical and patient-centered outcomes of cerebrovascular disorders.[2]

Thyroid hormone concentrations fluctuate in the acute phase of cerebrovascular disease[3]; therefore, it is difficult to estimate whether measurement of thyroid hormone concentrations at single time point of acute disease phase mirrors preceding thyroid axis functioning, represents acute thyroid axis response, or maybe represents new (temporally or permanent) hormonal balance. Also, medications (e.g., dexamethasone and dopamine) and diagnostic/therapeutic interventions commonly used in the acute stroke setting can interfere with thyroid gland functioning. For example, iodine-based contrast agents used for diagnostic imaging and endovascular interventions can cause acute transient fluctuations of thyroid hormone concentrations.[4] Furthermore, endovascular procedures and surgical interventions can predispose for fluctuations of thyroid hormone concentrations.[5] Triiodothyronine (T3) to thyroxin (T4) ratio is an index of peripheral T4 to T3 conversion via deiodination that can be impaired in

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

acute disease[2]; therefore, it would be interesting to see whether T4/T3 was associated with fatigue symptom severity.

1. Wang J, Li F, Xiao L, et al. Depressed TSH level as a predictor of poststroke fatigue in patients with acute ischemic stroke. Neurology 2018;91:e1971–e1978.
2. Bunevicius A, Iervasi G, Bunevicius R. Neuroprotective actions of thyroid hormones and low-T3 syndrome as a biomarker in acute cerebrovascular disorders. Expert Rev Neurother 2015;15:315–326.
3. Zetterling M, Engström BE, Arnardottir S, Ronne-Engström E. Somatotropic and thyroid hormones in the acute phase of subarachnoid haemorrhage. Acta Neurochir (Wien) 2013;155:2053–2062.
4. Rhee CM, Bhan I, Alexander EK, Brunelli SM. Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism. Arch Intern Med 2012;172:153–159.
5. Bunevicius A, Deltuva V, Tamasauskas S, et al. Low triiodothyronine syndrome as a predictor of poor outcomes in patients undergoing brain tumor surgery: a pilot study: clinical article. J Neurosurg 2013;118:1279–1287.

Editors' note: Concussion Biomarkers Assessed in Collegiate Student-Athletes (BASICS) I: Normative study

In the article "Concussion Biomarkers Assessed in Collegiate Student-Athletes (BASICS) I: Normative study", Asken et al. measured various concussion-related serum biomarkers in 415 nonconcussed collegiate athletes without recent exposure to head impacts and found that they expressed these markers in variable concentrations, depending on demographic factors such as sex and race, with poor test-retest reliability. In response, Dr. Satyarthee reviews some characteristics for an ideal serum biomarker for concussion and notes that the study did not evaluate the relationship of the tested biomarkers with a variety of other comorbid conditions. Replying to these comments, the authors agree that a broad limitation of current brain injury biomarker research is the uncertain influence of comorbid host factors that may affect biomarker concentrations. However, they note that many of the factors mentioned by Dr. Satyarthee such as malnutrition are rare in university athletes. They note that recognizing differences in demographics and comorbidities is important when seeking to translate brain injury biomarker research across different populations, such as sports-related injury in youth vs traumatic brain injury in middle age.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
Neurology® 2019;93:564. doi:10.1212/WNL.0000000000008143

Reader response: Concussion Biomarkers Assessed in Collegiate Student-Athletes (BASICS) I: Normative study

Guru Dutta Satyarthee (New Delhi)
Neurology® 2019;93:564–565. doi:10.1212/WNL.0000000000008145

Asken et al.[1] assessed a probable serum marker of concussion. Previously, I noted that the ideal serum biomarker can be clinically used to stratify traumatic concussion injury according to graded severity level, aid in confirmation of diagnosis, predict adverse secondary injury events including clinical worsening, predict the need of continuity of medical or neurosurgical intervention, guide appropriate application and modification of various treatment modalities, predict effectiveness of management methods, and predict prognostic outcome. Furthermore, its trend of serum level course over days, factors affecting serum level and relation over course of concussion management, should be well known.[2]

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

Asken et al. should be commended for making a preliminary attempt to find a probable biomarker of concussion; however, the study definitely lacks analysis of affecting biomarker level with drug interaction, normal physiologic level in pregnancy, lactation, changes with various age groups, malnutrition stage, obesity, various comorbid illnesses such as diabetes, hypertension, and suffering repeat brain injury.

1. Asken BM, Bauer RM, DeKosky ST, et al. Concussion Biomarkers Assessed in Collegiate Student-Athletes (BASICS) I: normative study. Neurology 2018;91:e2109–e2122.
2. Satyarthee GD. Biomarker-based targeted therapy of traumatic brain injury: from prehospital care to in-hospital care to rehabilitation. World Neurosurg 2017;103:939–941.

Author response: Concussion Biomarkers Assessed in Collegiate Student-Athletes (BASICS) I: Normative study

Breton M. Asken (Gainesville, FL)
Neurology® 2019;93:565. doi:10.1212/WNL.0000000000008144

Dr. Satyarthee nicely characterizes the potential roles of an ideal serum biomarker of brain injury and a broad limitation of current brain injury biomarker research: the unknown influence of factors unrelated to brain injury on biomarker concentrations. Concussion Biomarkers Assessed in Collegiate Student-Athletes (BASICS) I addressed how sex and race affected serum biomarker concentrations in nonconcussed university athletes.[1] BASICS II then evaluated how history of brain trauma affected baseline biomarker concentrations in the same healthy group.[2] Sex and race significantly affected serum biomarker levels, whereas history of concussion (single or repeated) and collision sport exposure did not. Pregnancy, malnutrition, and other comorbid medical conditions may also affect serum biomarker circulation, but such factors are exceedingly rare in university athlete samples compared with general civilian populations.

Study samples dictate the relative importance of predictors and outcomes of interest. Dr. Satyarthee's previous editorial[3] addressed a study of middle-aged patients with severe traumatic brain injury.[4] Such studies fundamentally differ from those evaluating samples exposed to sport-related concussion and/or repetitive subclinical trauma in collision sports. Recognizing these differences (e.g., typical age of injury, injury severity, and comorbid risks) is essential when translating research across disparate populations. Regardless, we agree that advancing brain injury biomarkers toward clinical use requires nuanced appreciation for the complexities of pathophysiology, biomarker kinematics, clinical symptoms, and patient-specific mediators.

1. Asken BM, Bauer RM, DeKosky ST, et al. Concussion Biomarkers Assessed in Collegiate Student-Athletes (BASICS) I: normative study. Neurology 2018;91:e2109–e2122.
2. Asken BM, Bauer RM, DeKosky ST, et al. Concussion BASICS II: baseline serum biomarkers, head impact exposure, and clinical measures. Neurology 2018;91:e2123–e2132.
3. Satyarthee GD. Biomarker-based targeted therapy of traumatic brain injury: from prehospital care to in-hospital care to rehabilitation. World Neurosurg 2017;103:939–941.
4. Hatefi M, Behzadi S, Dastjerdi MM, et al. Correlation of homocysteine with cerebral hemodynamic abnormality, endothelial dysfunction markers, and cognition impairment in patients with traumatic brain injury. World Neurosurg 2017;97:70–79.

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

Reader response: Financial relationships between neurologists and industry: The 2015 Open Payments database

Nathaniel M. Robbins (Lebanon, NH) and Mark J. Meyer (Washington, DC)
Neurology® 2019;93:566. doi:10.1212/WNL.0000000000008146

Drs. Ahlawat and Narayanaswami[1] detailed the extent of industry-related financial interests among neurologists captured in the Open Payments (OP) database. Industry-related conflicts of interests (COIs) widely influence neurologic education, research, and clinical practice.[2] Industry-funded trials often reach different conclusions than non-industry-funded trials,[3] and even small gifts to physicians can influence their prescribing practices.[4] Despite the OP database's shortcomings,[5] it is an important step for 2 reasons. First, disclosure only mitigates COI if the disclosed information is widely and publicly available. Patients are generally not aware of their doctors' financial relationships.[6] We hope OP will improve transparency. Second, the resulting social pressure from this transparency could lead to divestment from financial COI. Full disclosure is an important step towards mitigating COI, but does not redress subconscious biases that nearly invariably accompany financial relationships[2]; COI avoidance is often preferable. To investigate OP's effects on divestiture, we reviewed all neurologists in OP from 2013 to 2016. Of 9,505 neurologists in 2013 (OP's first year), 13 (0.07%) had ownership or investment interests totaling $26,610,645 (mean $2,800; median $65,975; maximum $24,949,811. In 2016, 16 of 11,105 neurologists had ownership and investment interest (0.09%) totaling $2,103,947 (mean $191; median $41,497; maximum $700,521). Perhaps OP is having an effect, but more research is required.

1. Ahlawat A, Narayanaswami P. Financial relationships between neurologists and industry: the 2015 Open Payments database. Neurology 2018;90:1063–1070.
2. Robbins NM. Ethical issues pertaining to conflicts of interest between neurologists and the pharmaceutical and medical device industries. Semin Neurol 2018;38:589–598.
3. McCambridge J, Hartwell G. Has industry funding biased studies of the protective effects of alcohol on cardiovascular disease? A preliminary investigation of prospective cohort studies. Drug Alcohol Rev 2015;34:58–66.
4. DeJong C, Aguilar T, Tseng CW, et al. Pharmaceutical industry-sponsored meals and physician prescribing patterns for medicare beneficiaries. JAMA Intern Med 2016;176:1114–1122.
5. Bernat JL, Swash M. Relationships between neurologists and industry. Neurology 2018;90:1047–1048.
6. Pham-Kanter G, Mello MM, Lehmann LS, Campbell EG, Carpenter D. Public awareness of and contact with physicians who receive industry payments: a national survey. J Gen Intern Med 2017;32:767–774.

This article has been republished with corrections from the original version (Neurology 2018;90:1063–1070). See http://links.lww.com/WNL/A975 for a version with errors highlighted.

CORRECTION

Reader response: Financial relationships between neurologists and industry: The 2015 Open Payments database

Neurology® 2019;93:566. doi:10.1212/WNL.0000000000008138

The Disputes & Debates comment "Reader response: Financial relationships between neurologists and industry: The 2015 Open Payments database" by Robbins & Meyer,[1] is republished in this issue.[2] The authors discovered an error in how they merged the "Ownership and Investment" dataset with the remainder of the Open Payments data. The error changed the Ownership numbers, but did not change the conclusions. The authors regret the error.

References

1. Robbins NM, Meyer MJ. Reader response: Financial relationships between neurologists and industry: the 2015 Open Payments database. Neurology 2019;92:351.
2. Robbins NM, Meyer MJ. Reader response: Financial relationships between neurologists and industry: the 2015 Open Payments database. Neurology 2019;93:566.

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

Reader response: Financial relationships between neurologists and industry: The 2015 Open Payments database

Neurology 2019;93;566
DOI 10.1212/WNL.0000000000008138