To the Editor:

It was with great interest that we read the recent original article by Alkhachroum et al. We have several points we would like to make about their study. To combat heterogeneity in terminology, the American Clinical Neurophysiology Society published a guideline with standardized nomenclature for the classification of critical care EEG patterns after years of testing, revision, and public review.1 Although the current article is on generalized periodic discharges (GPDs) and the authors report using the American Clinical Neurophysiology Society criteria, the exemplar figure of GPDs with triphasic morphology (Fig. 1A) only demonstrates 2 to 3 discharges in a row. This falls short of the minimum of six discharges to meet the American Clinical Neurophysiology Society criteria for a periodic pattern.2 In addition, the authors do not use the American Clinical Neurophysiology Society definition of triphasic morphology, but rather provide their own. To further complicate matters, many of the discharges in their figure of GPDs without triphasic morphology (Fig. 1B) do in fact have triphasic morphology, even by their own definition. This has been highlighted with a sample of their “non-triphasic” EEG below (Figure 1). Thus, it is unclear how these definitions were applied and suggests that there were other criteria, such as duration or prevalence of the pattern, sharpness, or presence of other EEG findings such as seizures, that the readers incorporated (consciously or not) when determining whether a pattern qualified as “triphasic.” It is stated that the electroencephalographers were masked to clinical data, but it does not state that they were masked to the remainder of the EEGs (such as presence or absence of seizures).

The remaining authors have no conflicts of interest to disclose.

L. J. Hirsch is the lead author of the American Clinical Neurophysiology Society’s guideline on standardized critical care EEG terminology. The American Clinical Neurophysiology Society published a guideline with standardized nomenclature for the classification of critical care EEG patterns after years of testing, revision, and public review.1 Although the current article is on generalized periodic discharges (GPDs) and the authors report using the American Clinical Neurophysiology Society criteria, the exemplar figure of GPDs with triphasic morphology (Fig. 1A) only demonstrates 2 to 3 discharges in a row. This falls short of the minimum of six discharges to meet the American Clinical Neurophysiology Society criteria for a periodic pattern.2 In addition, the authors do not use the American Clinical Neurophysiology Society definition of triphasic morphology, but rather provide their own. To further complicate matters, many of the discharges in their figure of GPDs without triphasic morphology (Fig. 1B) do in fact have triphasic morphology, even by their own definition. This has been highlighted with a sample of their “non-triphasic” EEG below (Figure 1). Thus, it is unclear how these definitions were applied and suggests that there were other criteria, such as duration or prevalence of the pattern, sharpness, or presence of other EEG findings such as seizures, that the readers incorporated (consciously or not) when determining whether a pattern qualified as “triphasic.” It is stated that the electroencephalographers were masked to clinical data, but it does not state that they were masked to the remainder of the EEGs (such as presence or absence of seizures).

Furthermore, it is unclear what was included as a seizure. From Table 2, the inference is that only 26/92 patients had either a recorded electrographic or EEG-verified electro-clinical seizure. This infers that 66/92 seizures were unrecorded clinical seizures based on chart review. If clinical seizures prompted EEG recording in the first place, and if some of these were treated with iatrogenic suppression-burst, this could have further increased this group’s association with seizures.

The study definition of electrographic seizure was not clear. The importance of this arises when again considering Fig. 1b. The figure demonstrates GPDs that are well established at 1.5 to 2 Hz. If, for example, the modified Salzburg criteria for electrographic seizures were applied, then this pattern would only need to increase to 2.5 Hz for 10 seconds to meet the definition of a definite seizure.3 This is being pointed out not as a proposed flaw of either the Salzburg criteria or this article, but mainly to raise awareness of the difficulties that classification sometimes carries, including leading to further circular logic.

The authors are commended for making efforts at tackling a debate that has spanned half a century. However, more work remains to be conducted before any clinical conclusions can be made based on waveform morphology alone.

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FIG. 1. Highlighted sample of the authors’ Figure 1b “non-triphasic” example showing waves that qualify as triphasic by their own definition, and by most definitions.

These points hold critical implications about the study’s primary outcome of comparative seizure rate. It cannot be purely the morphology of the discharge that determines epileptogenicity. In the study of 4,772 patients by Rodriguez-Ruiz et al., GPDs were associated with seizures in a frequency (cycles/second)-dependent manner, only reaching significant association with seizures when the GPDs reached 1.5 per second or faster.2 In addition, increased prevalence of GPDs was associated with increased seizure rates (abundant/continuous: 23% with OR 2.90, P = <0.001; frequent: 15%; rare/occasional: 8%; eTable3 in the Supplement).2 Returning to the article by Alkhachroum et al., if all patients in the triphasic morphology group had periodic patterns with comparatively lower prevalence or slower frequency, these factors alone could be sufficient to explain the lower seizure rate. In addition, the seizure rate of 92% in the group without triphasic morphology is striking and discordant with previous studies.2,3

It is important to note that the conclusions of the current study differ from that of Foreman et al.1 In the study by Foreman et al., there were 11 reviewers from multiple centers (rather than two from one center), and reviewers were masked to the remainder of the EEGs, by being provided only short segments of their prolonged continuous EEG recordings. That more methodologically rigorous study showed that the rate of seizures was identical in those with GPDs with triphasic morphology (25%) compared with those with GPDs without triphasic morphology (26%).3 The concerns with heterogeneity are also expressed regarding possible augmentation of the seizure rate in the nontriphasic group. It was surprising that suppression-burst was included as a generalized periodic pattern. Suppression-burst varies substantially from GPDs, especially regarding the associated seizure rate (32% with suppression-burst vs. 17% with GPDs in one study4).

LETTERS TO THE EDITOR

Generalized Periodic Discharges With and Without Triphasic Morphology

REFERENCES

In Reply:
Thank you for the opportunity to respond to the letter from Dr. Fong et al. to explain some aspects of our methodology and to discuss the topic of generalized periodic discharges (GPDs) and triphasic waves (TWs) in our article published in JCN. We read the letter with great interest and would like to thank the authors for taking the time to discuss this challenging topic.

We indeed agree with many of the criticisms included in their letter: the reviewers were not masked to the rest of the EEGs; therefore, we agree with the authors that this should have been taken into consideration. In addition, burst-suppression varies substantially from GPDs; therefore, the data could be reanalyzed excluding periodic burst-suppression discharges.

We agree that there are significant problems with both ACNS and our own definitions of TWs. The morphology of triphasic waves has been defined by 3 phases, negative—positive—negative, or 2 phases, negative—positive. These waveforms are defined by polarity, assuming “positive” and “negative” polarities as downward and upward deflections, respectively. This is incorrect because an upward deflection can be caused by a positive and a negative generator. Also, the morphology of TW is dependent on the montage used for analysis. Therefore, the best way to define a TW morphology is using upward and downward deflections in a given channel and a given montage.

It is correct that we did not necessarily follow ACNS recommendations to define TWs. We believe Committee definitions should be challenged because imposition of definitions may prevent advances in the research field. The study by Foreman et al. is a rigorous study, which showed that using their definition of TWs, the rate of seizures was identical to those with GPDs with triphasic morphology versus non-triphasic morphology. Nevertheless, we did find a significant difference using our criteria to define TWs, which does not necessarily mean that our criteria to define TWs are wrong, but may imply that our criteria are more useful.

We did not study the association between the frequency of GPDs and the increased seizure rate, but we agree that it should have been taken into account and should be studied in the future.

Our classification of GPDs with and without triphasic morphology was based on agreement between rater 1 and rater 2. Rater 1 and rater 2 applied the criteria defined in the methodology to differentiate records with or without TW morphology. However, when classifying a given record, rater 1 and rater 2 considered the general gestalt of the EEG and then decided how to classify the recording. Only analyzing selected channels in a given montage results in an incomplete analysis of the EEG. It is important to note that EEG interpretation is frequently subjective. For example, although there are general principles that we follow to define a sharp wave, the classification of activity (indicative of epileptogenesis) or nonepileptogenic sharp transients often varies depending on the subjective interpretation of the reviewer. We believe that differentiating between GPDs with and without triphasic patterns is extremely challenging in both clinical practice and in the research setting even when using standardized nomenclature and definitions.

We agree that seizure risk cannot be purely based on the morphology of a GPD. We believe that other factors such as history of epilepsy or focal abnormalities on EEG (as shown in our article) are epileptogenic factors to consider, in addition to what was described in the study by Rodriguez-Ruiz et al. The use of an antiepileptic trial may help recognize epileptogenic GPDs regardless of the pattern morphology.

In our study, patients in the seizure group were observed for 6—9 days. In the study by Foreman et al., two 30-minute segments of each continuous EEG recording were selected (one for GPDs and one for possible seizure activity). We also excluded patients with anoxic brain injury. This may explain as well the difference in seizure rate in our cohort when compared with the study by Foreman et al.

We appreciate the authors’ time and effort to address this important topic and the methodological points that they brought to our attention.

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