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Assessing quantitative EEG spectrograms to identify non-epileptic events

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ABSTRACT – *Aims*. To evaluate the sensitivity and specificity of quantitative EEG (QEEG) spectrograms in order to distinguish epileptic from non-epileptic events.

Methods. Seventeen patients with paroxysmal non-epileptic events, captured during EEG monitoring, were retrospectively assessed using QEEG spectrograms. These patients were compared to a control group of 13 consecutive patients (ages 25-60 years) with epileptic seizures of similar semiology. Assessment of raw EEG was employed as the gold standard against which epileptic and non-epileptic events were validated. QEEG spectrograms, available using Persyst 12 EEG system integration software, were each assessed with respect to their usefulness to distinguish epileptic from non-epileptic seizures. The given spectrogram was interpreted as indicating a seizure if, at the time of the clinically identified event, it showed a visually significant change from baseline.

Results. Eighty-two clinically identified paroxysmal events were analysed (46 non-epileptic and 36 epileptic). The "seizure detector trend analysis" spectrogram correctly classified 33/46 (71%) non-epileptic events (no seizure indicated during a clinically identified event) *vs*. 29/36 (81%) epileptic seizures (seizure indicated during a clinically identified event) (p=0.013). Similarly, "rhythmicity spectrogram", FFT spectrogram, "asymmetry relative spectrogram", and integrated-amplitude EEG spectrogram detected 28/46 (61%), 30/46 (65%), 22/46 (48%) and 27/46 (59%) non-epileptic events *vs*. 27/36 (75%), 25/36 (69%), 25/36 (69%) and 27/36 (75%) epileptic events, respectively.

Conclusions. High sensitivities and specificities for QEEG seizure detection analyses suggest that QEEG may have a role at the bedside to facilitate early differentiation between epileptic seizures and non-epileptic events in order to avoid unnecessary administration of antiepileptic drugs and possible iatrogenic consequences.

Key words: quantitative EEG, psychogenic non-epileptic seizures, seizure detection trend, PNES, jerking, shaking

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Psychogenic non-epileptic seizures (PNES) commonly mimic clinically as epileptic seizures. They frequently present as episodes of atypical motor activity with alterations of behaviour and sensation. However, unlike epileptic seizures, PNES do not reflect excessive or abnormal synchronous neuronal activity in the brain. Instead, PNES have been defined as physical manifestations of psychological disturbances and/or emotional responses (Benbadis, 2005). It has been reported that PNES may be diagnosed in 20-30% of patients evaluated for intractable seizures at epilepsy centres (Benbadis, 2005). Consequently, failure to detect PNES may lead to significant public health consequences by exposing individuals to unnecessary antiepileptic drug (AED) treatment, as well as unnecessary intubation, *etc*. According to one study, 54-69% of seemingly epileptic patients diagnosed with PNES had been unnecessarily treated with AEDs (Benbadis, 1999). Video-EEG is considered to be the gold standard for the diagnosis of PNES. Nevertheless, clinically distinguishing non-epileptic from epileptic events can be difficult (Bodde *et al.,* 2009). Indeed, nearly one third of patients with PNES presenting as episodes of prolonged hypermotor activity may be incorrectly diagnosed with status epilepticus. Not only does such misdiagnosis increase unnecessary administration of AEDs and sedative medications, it heightens the risk of iatrogenic harm and increases other medication-induced complications (*e.g.* cardiorespiratory arrest from excessive medication and other invasive procedures) (Walker *et al.,* 1996; Reuber *et al.,* 2004).

QEEG is a visual representation of compressed mathematically raw EEG. It processes digitally recorded EEG and highlights the specific waveform into a format that elucidates relevant information (Nuwer, 1997). It is a quantitative measurement of specific EEG properties (frequency, amplitude, rhythmicity, and power) and is a transformation of the raw EEG signal into numerical parameters. It can also be described as a signal analysis of the input from the various EEG electrodes that is displayed in power spectral properties. Multiple tools, including the rhythmicity spectrogram, FFT spectrogram, and computerized analysis algorithm (*e.g.* seizure detection), not only reduce the time associated with analysis of the complete continuous EEG data but help in the focused review of EEG epochs of potential interest. QEEG also helps by visualizing background abnormalities and aids in detecting interictal epileptiform transients and seizures (Haider *et al.,* 2016). QEEG can also be helpful for bedside personnel and physicians not trained in electrophysiology to potentially recognize significant EEG changes and seizure detection (Scheuer and Wilson, 2004).

A novel technique is presented to rapidly assess patients with PNES, while on continuous EEG monitoring, by employing QEEG analysis seizure detection trend and four spectrograms (alone and in combination).

Materials and methods

Recorded data

The study was approved by the Institutional Review Board of Montefiore Medical Center, and a waiver of informed consent was granted. A clinical database was searched to identify 17 successive adult patients (aged 25-60 years) who were diagnosed with non-epileptic events captured during continuous EEG monitoring between September 2016 and January 2017. Amongst the 17 patients in the non-epileptic cohort, almost half, 8/17 (47%), presented with "new onset seizure", and 9/17 (53%) previously carried a diagnosis of epilepsy. Clinical diagnostic pointers to suspect non-epileptic events, including multiple emergency room visits, acute stress in life, switching between multiple physicians, and suspicious clinical events, were suspected in 8/17 (47%) of the patients. None of these patients had continuous EEG monitoring in the past. A control group, consisting of 13 consecutively monitored patients with clinically overt epileptic events was also identified.

EEG review

EEG records of clinical events for all 30 patients were reviewed. Raw EEG tracings were analysed using the conventional 10-20 international placement system and digital recordings were evaluated by Board-certified neurologists trained in evaluating Persyst 12 EEG System Integration QEEG software. The given spectrogram was interpreted as indicating a seizure if, at the time of the clinically identified event, it showed a visually significant change from baseline.

The clinically identified events were classified as epileptic seizures (ES) when associated with EEG changes lasting >10 seconds and showing evolution in frequency, spatial distribution, or morphology (Hirsch *et al.,* 2005). Diagnoses of non-epileptic seizures required the recording of at least one typical clinical event during the EEG monitoring. Final diagnoses of PNES were defined by the absence of electrographic activity immediately prior to or during a typical event with observed clinical manifestations and absence of:

– neurological disorder;
– incapacitating or progressive physical illness;
– cardiorespiratory difficulty (Betts and Boden, 1992).

We compared this classification with the following Persyst 12 EEG System Integration QEEG software measures:
– "Seizure detector trend" spectrogram. The seizure detector algorithm combines multiple inputs into a probability on a second-by-second basis. It provides a discrete value of zero or one depending on whether a seizure has been detected.
– "Rhythmicity spectrogram". This displays a density spectral array of frequency and power as a function of time. The x axis displays time, y axis represents frequency, and the z axis demonstrates power characterized as a colour scale.
– FFT spectrogram. This is a visual representation of the evolution of the frequency domain of the EEG over time derived from a fast Fourier transform. Amplitude is represented by colour, frequency by position on the y axis, and time by position on the x axis.
– Asymmetry relative spectrogram. This displays visual representation of power differences between two hemispheres at discrete frequencies as a function of time. Time is displayed on the x axis and percent absolute asymmetry on the y axis.
– "Amplitude EEG (aEEG) spectrogram". Amplitude characteristics of a filtered, rectified representation of the EEG signal are displayed as a function of time. The x axis represents time, and the y-axis displays aEEG amplitude.

Statistical analysis

The sensitivity and specificity of detection of the non-epileptic events were calculated by comparing the seizures detected by individual spectrograms using QEEG amongst the study group and the control group. A true positive was defined as a non-epileptic seizure detected as artefact by the QEEG (correctly classified as PNES). A false positive (type I error) was assigned to non-epileptic events highlighted as seizure by the QEEG. False negatives (type II error) were true epileptic seizures, not detected by the QEEG. True negatives were epileptic seizures identified as seizures by the QEEG. A two-tailed *p* value using the McNemer test was calculated to determine statistical significance.

Results

Forty-six non-epileptic paroxysmal events from 17 patients and 36 epileptic seizures amongst 13 patients were captured and categorized based on continuous EEG monitoring. The clinical events and QEEG findings amongst the non-epileptic and epileptic seizure cohort are presented in *table 1*. The sensitivities, specificities, and *p* values for different spectrograms regarding the differentiation between PNES from ES are presented in *table 2*. QEEG seizure detection trend analysis correctly classified 33/46 (71%) non-epileptic events (no seizure highlighted during a clinically identified event) *vs.* 29/36 (81%) epileptic seizures (seizure highlighted during a clinically identified event) (p=0.013).
The asymmetry relative spectrogram demonstrated a visually distinct departure from the baseline in 22/46 (48%) non-epileptic events *vs.* 25/36 (69%) epileptic seizures (p=0.47). Similarly, rhythmicity spectrogram, FFT spectrogram, and amplitude EEG spectrogram correctly classified 28/46 (61%), 30/46 (65%), and 27/46 (59%) non-epileptic events *vs.* 27/36 (75%) (p=0.096), 25/36 (69%) (p=0.87), and 27/36 (75%) (p=0.14) epileptic events, respectively (*figure 1*).
The QEEG seizure detection trend evidenced greatest discriminative power for 31/36 (86%) when clinical manifestations during events were non-rhythmic body jerking (*figure 2B*), whole-body stiffening with some jerking (*figure 2C*), and whole-body tonic posturing (*figure 2D*). Poor discriminative power (detecting non-epileptic events as seizures) for 2/10 (20%) was evident for events with prolonged duration (>5 minutes) and rhythmic body jerking (*figure 2A*). The false positive rate (non-epileptic events highlighted as seizure according to QEEG) was 28% (*i.e.* 13 of 46 non-epileptic events were incorrectly identified as seizures).
In contrast, the asymmetry relative spectrogram demonstrated poorest discriminative power with a false positive rate (non-epileptic events highlighted as seizure according to QEEG) of 24/46 (52%). The factor most responsible for decreasing its sensitivity was misattribution of generalized rhythmic body shaking as seizures (*figure 2A*).
QEEG seizure detection trend correctly classified 29/36 (81%) epileptic events in the control group as seizures (correctly identifying 29 of 36 events as epileptic).

Discussion

Evidence of high sensitivity and specificity for QEEG analyses, discriminating non-epileptic events from seizures, suggests greater utility for its clinical application. QEEG may be employed at the bedside to facilitate early differentiation of PNES from ES in order to avoid unnecessary administration of AEDs. Forty-one percent of the 17 patients in this cohort were determined to have non-epileptic events and were treated with abortive antiepileptic medications during a clinical event while on continuous EEG monitoring. Furthermore, facilitating early discrimination of PNES from epileptic seizures avoids possible iatrogenic consequences.
There are multiple reported studies using various QEEG techniques, including aEEG displays performed

Table 1. Quantitative EEG analysis of patients with non-epileptic and epileptic events.

(A) Non-epileptic seizure cohort: non-epileptic seizures classified as seizure by various spectrograms							
Patient	No. of non-epileptic events	Seizure detection trend	Rhythmicity spectrogram	FFT spectrogram	Asymmetry spectrogram	aEEG spectrogram	Clinical manifestations
1	2	2	2	2	2	2	Whole-body rhythmic jerking
2	3	0	2	2	3	2	Whole-body stiffening
3	3	0	0	0	0	0	Shoulder jerk
4	3	2	2	2	2	2	Whole-body rhythmic jerking
5	2	0	0	0	2	0	Whole-body non-rhythmic shaking
6	2	0	0	0	1	1	Leg jerking
7	4	4	4	4	4	4	Whole-body rhythmic jerking
8	3	0	2	2	2	1	Tonic posturing
9	1	1	1	1	1	1	Whole-body non-rhythmic shaking
10	4	1	1	1	1	1	Whole-body non-rhythmic shaking
11	3	0	0	0	0	0	Whole-body non-rhythmic shaking
12	1	0	1	1	0	0	Minor shaking and unresponsiveness
13	1	0	1	1	1	1	Head jerking
14	3	0	0	0	1	0	Brief body jerks and grimacing
15	9	2	2	0	4	4	Whole-body non-rhythmic shaking
16	1	0	0	0	0	0	Whole-body non-rhythmic shaking
17	1	1	0	0	0	0	Whole-body rhythmic jerking

Table 1. (*Continued*) Quantitative EEG analysis of patients with non-epileptic and epileptic events.

(B) Epileptic seizure cohort: Epileptic seizures classified as seizure by various spectrograms							
Patient	No. of epileptic events	Seizure detection trend	Rhythmicity spectrogram	FFT spectrogram	Asymmetry spectrogram	aEEG spectrogram	Clinical manifestations
1	3	3	3	3	3	3	Whole-body jerking
2	1	1	1	1	1	1	Whole-body jerking
3	5	5	0	0	0	0	Jerking and tonic posturing
4	1	1	0	0	0	0	Jerking and tonic posturing
5	1	1	1	1	1	1	Whole-body jerking
6	3	1	1	1	1	1	Whole-body jerking
7	1	1	1	1	1	1	Whole-body rhythmic jerking
8	1	1	1	1	1	1	Body jerk and tonic posturing
9	4	3	4	4	3	4	Whole-body jerking
10	1	1	1	1	1	1	Whole-body jerking
11	5	4	5	5	5	5	Whole-body jerking
12	3	2	2	0	1	2	Body jerk and tonic posturing
13	7	5	7	7	7	7	Body jerk and tonic posturing

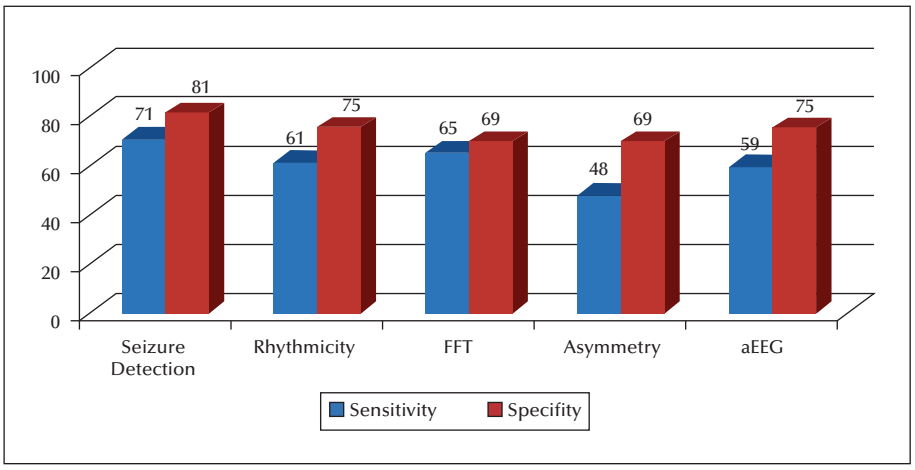

Figure 1. Specificities and sensitivities of QEEG spectrograms for detecting non-epileptic events.

Table 2. Relative specificity, sensitivity and *p* value for quantitative EEG using various spectrogram to differentiate non-epileptic from epileptic events.

		Non-epileptic group	Control group	Sensitivity	Specificity	*p* value
Total no. of events	82	46	36			
Seizure probability trend	Classified as seizure Classified as no seizure	13 (29%)^{FP} 33 (71%)^{TP}	29 (80%)^{TN} 7 (20%)^{FN}	71	81	0.0131
Rhythmicity spectrogram	Classified as seizure Classified as no seizure	18 (39%)^{FP} 28 (61%)^{TP}	27 (75%)^{TN} 9 (25%)^{FN}	61	75	0.096
FFT spectrogram	Classified as seizure Classified as no seizure	16 (34%)^{FP} 30 (65%)^{TP}	25 (69%)^{TN} 11 (31%)^{FN}	65	69	0.0871
Asymmetry spectrogram	Classified as seizure Classified as no seizure	24 (52%)^{FP} 22 (48%)^{TP}	25 (69%)^{TN} 11 (31%)^{FN}	48	69	0.4721
aEEG spectrogram	Classified as seizure Classified as no seizure	19 (41%)^{FP} 27 (59%)^{TP}	27 (75%)^{TN} 97 (25%)^{FN}	59	75	0.1407

TP: True positive (non-epileptic seizure detected as artefact by QEEG).
FP: False positive (non-epileptic events highlighted as seizure by QEEG).
TN: True negative (epileptic seizures identified as seizures).
FN: False negative (epileptic seizures not identified as seizures).

in the Neonatal Intensive Care Unit (NICU). These studies have a wide range of reported sensitivities for seizure identification that range from 26% to 76% (Shellhaas *et al.,* 2007; Shah *et al.,* 2008). A similar study conducted with neonates, using EEG envelope trend analysis, identified 88% of prolonged seizures, 40% of brief seizures, and 20% of slowly evolving seizures, with false-positive rates of 0-2 per hour (Abend and Dlugos, 2008). Another study in which QEEG spectrograms were employed to detect seizures in a paediatric population reported a sensitivity of 83% using a colour density spectral array (CDSA) and 81.5% using aEEG (Stewart *et al.,* 2010). A similar paediatric study assessed the factors affecting seizure detection using QEEG analysis. The authors used the envelop trend (ET) and compressed spectral array (CSA) for seizure identification in critically ill patients in the ICU. The study concluded that multiple factors affected accurate seizure detection including interpreter's experience, display size, and type of QEEG methods used (Akman *et al.,* 2011).

Apart from detecting seizures, QEEG has also been used in long-term monitoring of comatose patients. In all these studies, the sensitivity of specific spectrograms has been examined, but none of these studies have compared the relative sensitivity amongst the various spectrograms. These studies revealed high sensitivities for individual QEEG spectrograms detecting seizures. However, to our knowledge, there have not been any studies demonstrating comparable sensitivity of QEEG for discriminating paroxysmal clinical events as epileptic seizures *vs.* non-epileptic events.

In our study, rhythmicity and amplitude spectrograms revealed poor sensitivities for detecting non-epileptic events. Rhythmicity spectrograms assess amplitude in four user-defined frequency bands, spanning 1-25 Hz, whereas amplitude spectrograms do not depict frequency or rhythmicity information. However, both of these are based on amplitude of primary rhythmic EEG components. Conceivably, their poor sensitivities and specificities for detecting non-epileptic events may be attributable to high-amplitude artefacts generated during paroxysmal clinical events. False positives (non-epileptic events highlighted as seizure on QEEG) were highest for the asymmetry spectrograms. The latter reflects hemispheric asymmetry between homologous electrodes and frequencies in the vertical axis. Focal rhythmic or non-rhythmic shaking, body jerks, and asymmetric motor events may produce interhemispheric asymmetry that could explain this high false positive outcome.

In a previous study, time-frequency analysis of data from a wristband movement monitor was evaluated as a diagnostic tool to differentiate between epileptic and non-epileptic events. The study concluded that the coefficient of variation of limb movement frequency was significantly lower for the non-epileptic events compared to the epileptic events (median: 17.18% *vs.* 52.23%; $p<0.001$). Based on the study, the authors advised the use of a wristband movement monitoring device for outpatient monitoring of ambulatory patients (Bayly *et al.,* 2013). It is posited that the high sensitivity of QEEG seizure detector trend obtained in this study, for discriminating non-epileptic

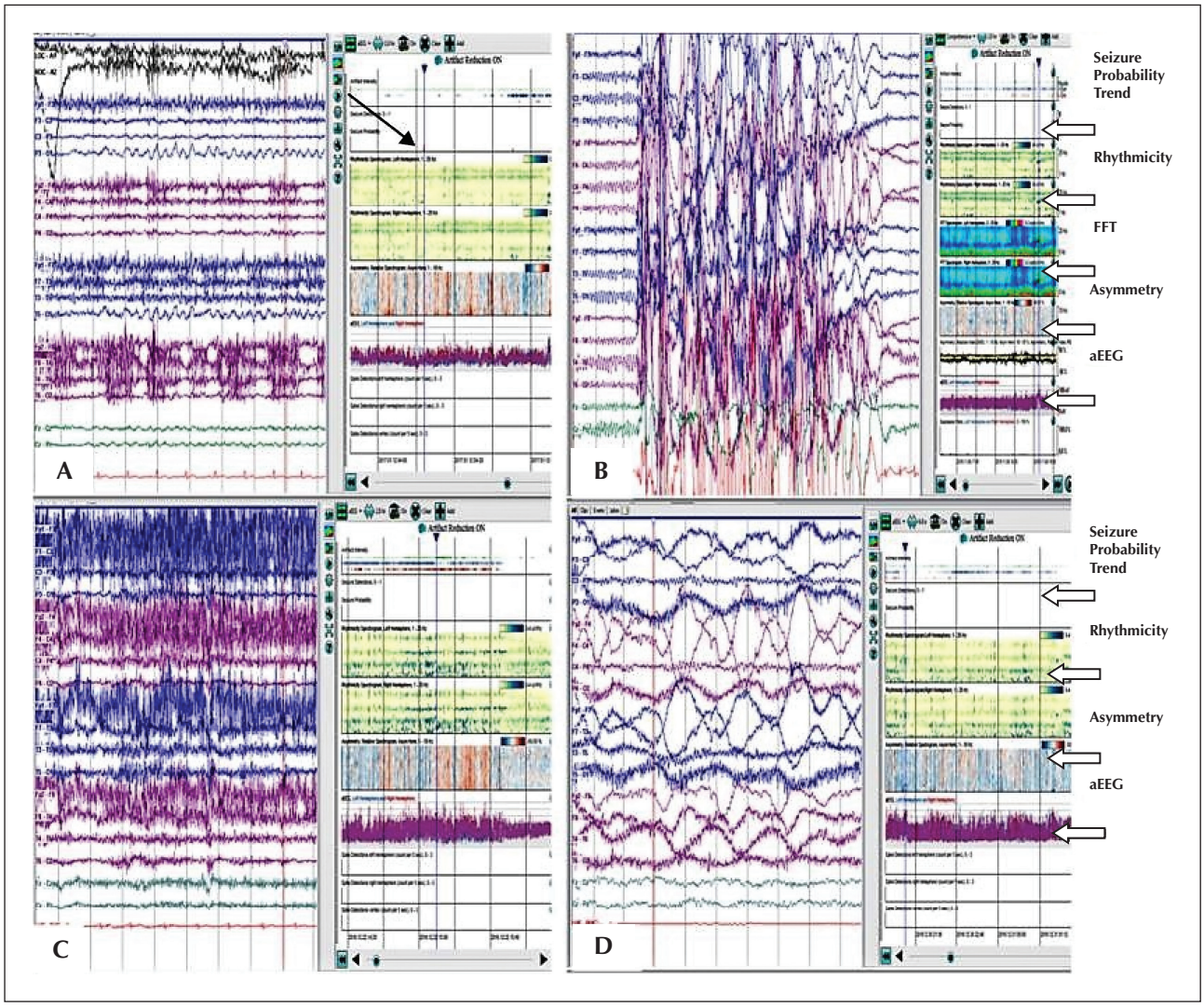

Figure 2. Quantitative EEG and raw EEG representation of various clinical manifestations in the non-epileptic patients.
(A) Raw EEG (left) showing quasi-rhythmic discharge over the central head regions; quantitative EEG (right) showing positive seizure detection; clinically, rhythmic head jerking is evident.
(B) Raw EEG (left) showing overlying muscle and movement artefacts; quantitative EEG (right) remains normal throughout; clinically, non-rhythmic whole-body jerking is evident.
(C) Raw EEG (left) showing overlying muscle artefact; quantitative EEG (right) remains normal throughout; clinically, whole-body stiffening with some jerking is evident.
(D) Raw EEG (left) showing overlying muscle artefact; quantitative EEG (right) remains normal throughout; clinically, whole-body tonic posturing is evident.

events from seizures, may have reflected the strength of its algorithm. The latter was constructed to incorporate inputs from multiple trends and combine them into probability values on a second-by-second basis. One of these trends, artefact intensity, may have particular value in recognizing hypermotor events as muscle artefact.

Our study was limited by the retrospective assessment of a relatively small number of epileptic and non-epileptic events. Additionally, because seizures for the control group patients were not classified by duration and focality (sensitivity of seizure detection differs based on duration and type of seizures), their interpretation based on QEEG may have been affected (Abend *et al.*, 2008). Furthermore, although the validity of seizures was based upon raw EEG evaluations by Board-certified neurologists trained in evaluating QEEG, the possibility that interrater reliability differences of interpretation contributed to error was not controlled.

Conclusion

High sensitivities and specificities for QEEG seizure detection analyses suggest that QEEG may have a role at the bedside to facilitate early differentiation between epileptic seizures and non-epileptic events in order to avoid unnecessary administration of AEDs and possible iatrogenic consequences. We will need multicentre prospective studies to assess whether it is more efficient to teach QEEG or video-EEG to the inexperienced bedside observer and whether QEEG adds to the ability of an experienced clinician to distinguish ES from PNES. □

Disclosures.
The authors have no conflict of interest to disclose.

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TEST YOURSELF

(1) What is quantitative electroencephalography?

(2) What is the gold standard for diagnosis of psychogenic non-epileptic seizures (PNES)?

(3) What are psychogenic non-epileptic seizures (PNES) and how do they manifest?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".