FULL-LENGTH ORIGINAL RESEARCH

Quantitative analysis of surface electromyography during epileptic and nonepileptic convulsive seizures

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Summary

Objective: To investigate the characteristics of sustained muscle activation during convulsive epileptic and psychogenic nonepileptic seizures (PNES), as compared to voluntary muscle activation. The main goal was to find surface electromyography (EMG) features that can distinguish between convulsive epileptic seizures and convulsive PNES.

Methods: In this case–control study, surface EMG was recorded from the deltoid muscles during long-term video–electroencephalography (EEG) monitoring in 25 patients and in 21 healthy controls. A total of 46 clinical episodes were recorded: 28 generalized tonic–clonic seizures (GTCS) from 14 patients with epilepsy, and 18 convulsive PNES from 12 patients (one patient had both GTCS and PNES). The healthy controls were simulating GTCS. To quantitatively characterize the signals we calculated the following parameters: root mean square (RMS) of the amplitude, median frequency (MF), coherence, and duration of the seizures, of the clonic EMG discharges, and of the silent periods between the cloni. Based on wavelet analysis, we distinguished between a low-frequency component (LF 2–8 Hz) and a high-frequency component (HF 64–256 Hz).

Results: Duration of the seizure, and separation between the tonic and the clonic phases distinguished at group-level but not at individual level between convulsive PNES and GTCS. RMS, temporal dynamics of the HF/LF ratio, and the evolution of the silent periods differentiated between epileptic and nonepileptic convulsive seizures at the individual level. A combination between HF/LF ratio and RMS separated all PNES from the GTCS. A blinded review of the EMG features distinguished correctly between GTCS and convulsive PNES in all cases. The HF/LF ratio and the RMS of the PNES were smaller compared to the simulated seizures.

Significance: In addition to providing insight into the mechanism of muscle activation during convulsive PNES, these results have diagnostic significance, at the individual level. Surface EMG features can accurately distinguish convulsive epileptic from nonepileptic psychogenic seizures, even in PNES cases without rhythmic clonic movements.

KEY WORDS: Convulsive seizures, Nonepileptic psychogenic seizures, Surface electromyography.

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The gold standard for diagnosing psychogenic nonepileptic seizures (PNES) is the video–electroencephalography (EEG) recording.[1] However, long-term video-EEG monitoring (LTM) is extremely resource-demanding[2] and not available worldwide. A number of adjunctive parameters can be used to assist in the diagnosis of PNES: postictal serum prolactin,[3] conversation analysis,[4–7] heart rate variability,[8] and accelerometry.[9]

The differential diagnosis of convulsive PNES is the epileptic, tonic–clonic seizure.[1] Previous studies on surface electromyography (EMG) during convulsive seizures showed that the mechanism of muscle activation during epileptic seizures was different from voluntary muscle activation: The tonic phase of generalized tonic–clonic seizures (GTCS) was characterized by a marked increase in amplitude-derived parameters, tonic seizures had a marked increase in frequency, and in both seizure types the coherence between the homologous muscles on the left and right sides was higher than during voluntary muscle activation.[10] Wavelet analysis demonstrated specific temporal dynamics of muscle activation during GTCS, best described by the ratio between the high frequency (HF; 64–256 Hz) and low-frequency (LF; 2–8 Hz) components.[11] The gradual seizure onset (buildup of EMG activity) was followed by a suppression of the LF component and increase in the HF component during the tonic phase, followed by a marked increase in the LF at the transition between the tonic and the clonic phases. This resulted in a clear HF/LF peak during the tonic phase. The duration of the EMG bursts of the clonic jerks was remarkably constant (0.2 s), and the duration of the silent periods between the clonic jerks increased exponentially during the clonic phase.[11] An automatic system implementing specific quantitative EMG features resulted in an accurate detection of the GTCS.[12]

Up to now, no data on quantitative EMG features during convulsive PNES have been published. We hypothesized that quantitative EMG features will differentiate between convulsive epileptic and convulsive PNES. In addition, we also wanted to compare the EMG features of convulsive PNES with volitional muscle activation in healthy controls simulating convulsive seizures.

Methods

Patients and seizures

Data from 25 consecutive patients admitted to the epilepsy monitoring unit (EMU) for diagnostic reasons or for presurgical investigation, who had convulsive PNES or GTCS registered in the EMU, were analyzed. Patients gave their informed consent prior to the admission to the EMU, and the study has been approved by the regional ethics committee.

Forty-six convulsive episodes were recorded in the EMU. All episodes were analyzed. Twenty-eight GTCS were recorded from 14 patients with epilepsy. Eighteen episodes with convulsive PNES were recorded from 12 patients. One of these patients had both GTCS (two episodes) and PNES (two episodes). The gold standard was the final conclusion on the video-EEG monitoring, by a panel of trained experts, including epileptologists and clinical neurophysiologists with experience in evaluating LTM recordings.

The patients with PNES (eight male; four female) were between 17 and 54 years old (mean 31.6; median: 26.5). The patients with GTCS (11 male, three female) were between 11 and 62 years old (mean 32.7; median 27.5). One patient had idiopathic generalized epilepsy (juvenile myoclonic epilepsy); all other patients had focal epilepsies with secondarily generalized tonic–clonic seizures.

In addition, 21 healthy controls simulated GTCS, as instructed by the authors, and after watching video recordings with examples of GTCS. After 10 s of maximal voluntary contraction, simultaneously in the antagonistic muscles, the subjects simulated the clonic phase for 60 s by successive epochs of maximal voluntary contraction and relaxation in all muscles. Each subject simulated five episodes, and the episode closest resembling a GTCS was chosen for further analysis. The control subjects (13 male; eight female) were between 6 and 54 years old (mean 26.7; median 26).

There was no significant difference concerning age and gender among the three groups.

Recordings

LTM recordings in the EMU included at least two EMG channels (silver/silver chloride 9-mm surface electrodes), in addition to 25 scalp EEG electrodes, electrocardiography (ECG), and (in three patients) respiration belts (chest and abdominal wall movement). EMG signals from the deltoid muscles on both sides were analyzed in all subjects. The active electrode was placed on the midpoint of the deltoid muscle belly, and the reference electrode was on the acromioclavicular joint, just proximal to the insertion of the muscle (monopolar setting). EMG signals were sampled with a frequency of 1,024 Hz, and anti-aliasing filter of 512 Hz. Signals were then high-pass filtered (2 Hz) with a finite impulse response filter.

Data analysis and evaluation

We calculated the EMG parameters that in previous studies proved to characterize epileptic convulsive seizures[10,11]: root mean square (RMS) of the amplitudes, median frequency (MF), coherence (between left and right side), and duration of the seizures, of the clonic EMG discharges, and of the silent periods between the clonic discharges. Based on wavelet analysis, we distinguished between an LF component (2–8 Hz) and an HF component (64–256 Hz), and we determined the HF/LF ratio throughout the clinical episodes. Comprehensive descriptions of calculating these parameters have been published previously.[10,11]

Because the RMS shows considerable inter-individual variability, we calculated a normalized RMS ratio (mean

RMS seizure/mean RMS during maximal voluntary contraction). Due to lack of compliance, we could record only maximal voluntary contraction in 10 patients (5 patients with PNES who had 6 seizures and 5 patients with epilepsy who had 12 seizures altogether).

Two authors (SB and IC) compared EMG parameters derived from convulsive PNES with GTCS and with simulated seizures, and compiled a set of EMG features that distinguished between epileptic and nonepileptic convulsive seizures (see Results).

Three authors (PJ, MF, and PW) reviewed the EMG signals and the calculated EMG parameters for all episodes of convulsive PNES and GTCS. These authors were blinded for all other clinical and neurophysiologic data. They had to classify the convulsive episodes as epileptic or nonepileptic, applying the set of EMG features described earlier. The consensus decision (choice made by at least two of the three blinded authors) was logged.

Statistics

We performed multivariate analysis of variance (MANOVA) for all subject-groups and the quantitative EMG parameters (RMS, MF, HF/LF-ratio, coherence) to test the null hypothesis that the values of each group are the same multivariate vector and that the observed difference is due to random chance. We then used Kruskal-Wallis test to assess the effect of the patient groups on the quantitative EMG parameters, because the distribution was not normal. As post hoc tests, for group comparisons we used the Mann-Whitney test, corrected for cumulated probabilities (Bonferroni). Because the duration of the simulated seizures was determined by the given instruction and it was the same for all control subjects, we did not include this parameter into the multivariate analysis; instead, we used the Mann-Whitney test to compare the seizure durations (as measured by the duration of EMG activity) between the groups of GTCS and PNES. For comparison of gender and of the occurrence of the observed EMG features chi-square test was used. Statistical analysis was carried out with MATLAB R2013b (MathWorks, Natick, MA, U.S.A.).

Results

Surface EMG differentiated well between GTCS, PNES, and the simulated seizures (Fig. 1). MANOVA rejected the null hypothesis that the observed difference is due to random chance ($d = 1$). Significant effect was found for the following quantitative EMG parameters: coherence ($p = 0.01$), HF/LF ratio ($p < 0.0001$), and RMS ($p < 0.0001$).

Duration

The duration of the simulated seizures was determined by the received instructions (70 s). In the PNES group, the duration of the EMG activation corresponding to the seizure (14–960 s; median 112 s) was longer than in the GTCS group (37–147 s; median 65 s; $p < 0.02$). However, this did not distinguish between the two groups at individual level: duration of 7 of the 18 PNES fell within the range of the GTCS duration.

Amplitude

RMS of the EMG amplitude (Fig. 1A–C) in the PNES group (0.02–0.3; median 0.08 mV) was significantly lower than in the simulated seizures (0.12–1.2; median 0.45 mV), and in turn, the RMS of the simulated seizures was significantly lower than in the GTCS group (0.27–2.7; median 1.16 mV; $p < 0.001$). Only one of the 18 episodes of PNES had RMS that fell within the range seen in GTCS. The subgroup analysis of the normalized RMS ratio gave similar results ($p < 0.01$), showing that the observed differences are not due to the interindividual variability.

Coherence

The coherence during the GTCS (0.06–0.32; median: 0.1) was higher as compared with PNES (0.005–0.39; median: 0.04) and with simulated seizures (0.04–0.11; median: 0.07; $p < 0.03$). However, this difference did not remain significant after Bonferroni correction. At the individual level, coherence was not useful for distinguishing between PNES and GTCS, as four episodes of PNES fell within the range of GTCS.

Frequency

MF calculated for the whole seizure epoch did not distinguish between the three groups. The HF/LF ratio calculated for the whole seizure epoch was smaller for PNES (0.3–13; median 2.3) than for the simulated seizures (6.7–39.3; median 16) and smaller than GTCS (7.3–61.3; median 20.6; $p < 0.0001$). As described earlier,[11] the HF/LF ratio showed a specific evolution in time throughout the GTCS: Following a gradual onset (buildup of EMG activity) a prominent HF/LF peak occurred during the tonic phase (Fig. 1A,D,G). This pattern of HF/LF dynamics was not observed in any of the PNESs or simulated seizures (Fig. 1; $p < 0.0001$).

Figure 2 shows that a combination of RMS and HF/LF ratio completely separates PNES from GTCS: $(14.74 - 4.74 * \text{RMS} - \text{HF/LF})$ is >0 for all GTCS and is <0 for all PNES.

Dynamics of the clonic phase

In all GTCS the tonic muscle activation was followed by a clonic phase (Fig. 3A) in which the EMG activity was interrupted by silent periods (SPs) with durations increasing exponentially toward the end of the seizure (Fig. 4A).[11] In only seven cases of PNES was the clonic phase separated from the tonic phase in the EMG recordings (Fig. 3B). In none of these cases of PNES did the temporal dynamics of the SPs show the exponential evolution seen in GTCS. The SPs had more constant duration, resulting in quasi-rhythmic movements (Fig. 4B). In 11 cases of PNES, the clonic jerks

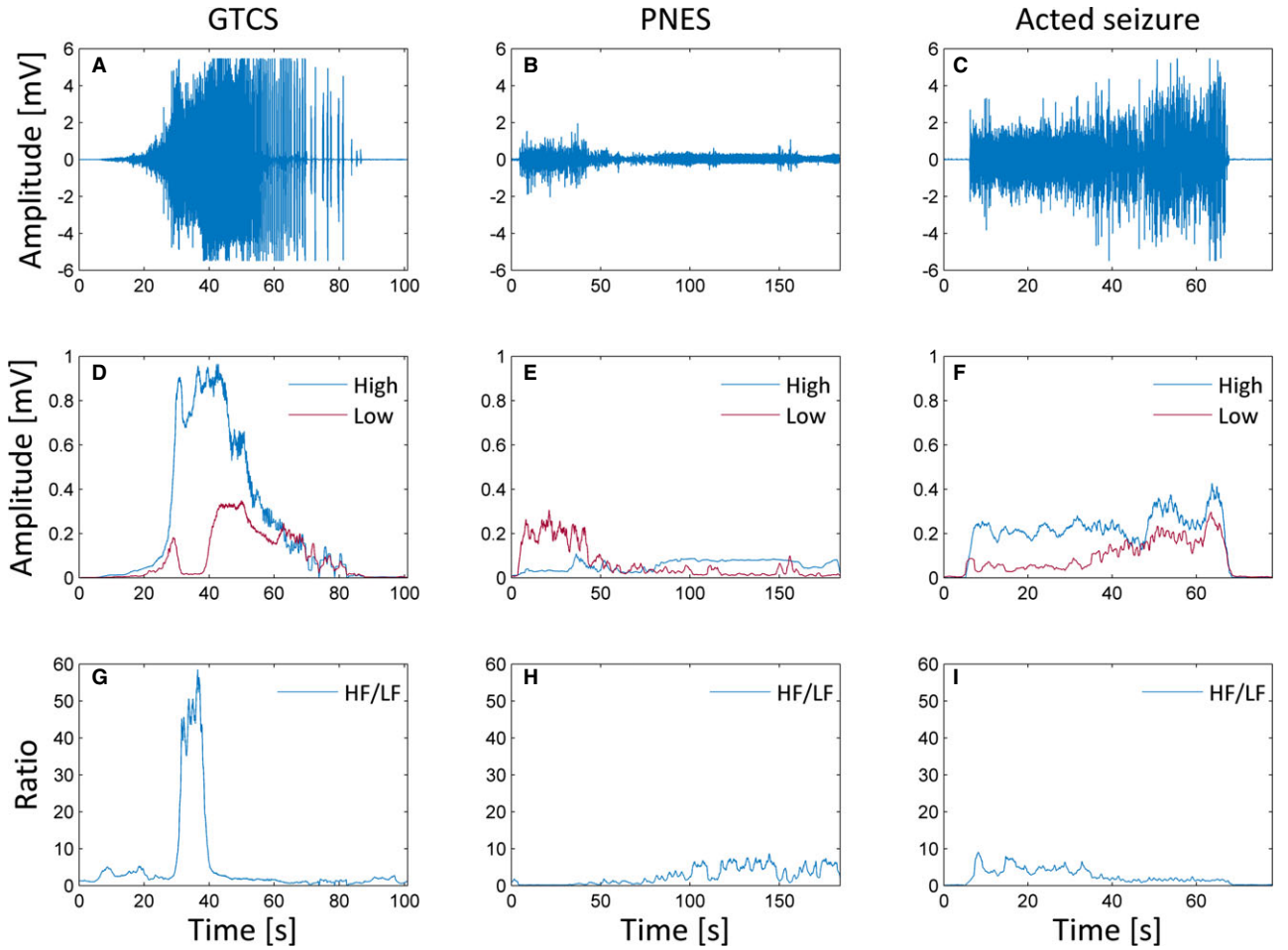

Figure 1.

Surface EMG recordings and plots of the HF and LF components and of the HF/LF ratio throughout GTCS (**A**, **D**, **G**), PNES (**B**, **E**, **H**), and simulated seizure (**C**, **F**, **I**). (**A**–**C**) The evolution of the EMG signal amplitude in the three types of seizures. Observe the gradual buildup of tonic EMG activity, followed by the well-identifiable clonic phase; this pattern was present in all GTCS, but not in the other two groups. (**D**–**F**) The evolution in time of the HF (64–256 Hz; blue line) and LF (2–8 Hz; red line) wavelet components. Please notice the marked increase in HF component, simultaneous with suppression of the LF component during the tonic phase of the GTCS. This pattern is not observed in the other two groups. (**G**–**I**) The evolution in time of the HF/LF ratio. A clear HF/LF peak is observed during the tonic phase of the GTCS. This is not present in the other two groups.

were intermixed with the tonic phase: The amplitude of the EMG discharges was waxing and waning, but there were no SPs in between, and this occurred throughout the seizure, not just at the end of the seizure (Fig. 3C).

The duration of the clonic EMG discharges between the SPs was longer for the simulated seizures (577–2,362; median 1,318 msec) as compared with the GTCS (158–321; median 206 msec) and with PNES (109–327; 143 msec; $p < 0.001$). There was a tendency for shorter clonic EMG discharges during PNES as compared with GTCS ($p = 0.05$); however, this did not remain significant after Bonferroni correction.

Blinded review

Based on these results, the following criteria were defined for distinguishing between GTCS and nonepileptic convulsive seizures: gradual onset of EMG activity, followed by high amplitude tonic phase showing a HF/LF peak; in case clonic phase was identified: exponential dynamics of the SPs. Three of the authors, blinded for all other data, reviewed the EMG recordings and the HF/LF plots for all GTCS and PNES (n = 46), presented in a random sequence. In a separate setting they reviewed the SP-dynamics plots for all GTCS and the cases of PNES that had SPs (n = 35), presented in a random sequence. The visual assessment of the EMG signals and the HF/LF plots (i.e., without considering the characteristics of the clonic phase) accurately differentiated between GTCS and PNES in all but one case (sensitivity: 97.2%). This was a case of PNES, categorized as GTCS. Visual assessment of the SP-dynamics plots of the cases with a clonic phase correctly differentiated between PNES and GTCS in all 35 cases. The case of PNES that was

categorized as GTCS based on the characteristics of the tonic muscle activation, had a clonic phase as well, and it was correctly classified as PNES when taking into consideration the dynamics of the clonic phase. Thus by combining the EMG features of both the tonic and the clonic phases, a sensitivity of 100% has been achieved. One patient had both GTCS (two episodes) and PNES (two episodes); all four episodes were correctly classified.

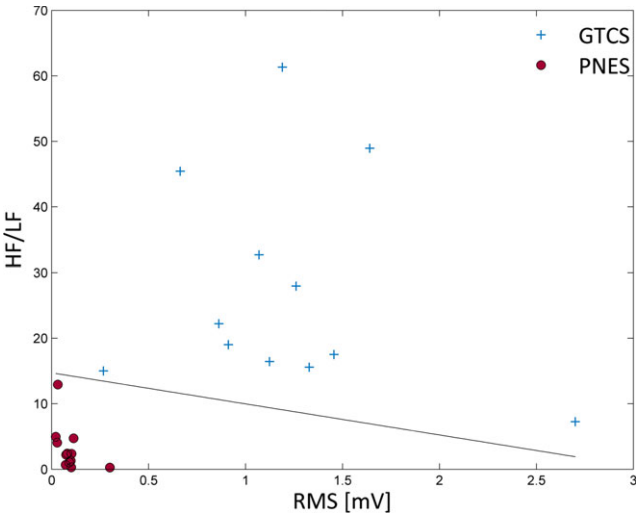

Figure 2.
Decision boundary for separating PNES from GTCS. The Y-axis represents the HF/LF ratio; the X-axis represents the RMS values. The red circles symbolize the PNES, whereas the blue + signs symbolize the GTCS. A complete separation between PNES and GTCS is achieved by a linear discriminator in the HF/LF versus RMS plot (HF/LF = −4.74*RMS + 14.74).
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Discussion

Our previous studies showed that the mechanisms of muscle activation during convulsive epileptic seizures are different from the voluntary muscle activation during simulated seizures.[10,11] Whereas PNES are often misunderstood as simulated seizures, in the present study we found that RMS of the EMG amplitude and the HF/LF ratio was different between PNES and simulated seizures. Our findings suggest that they are categorically different. In order to resemble GTCS as much as possible, the control subjects were instructed to produce maximal voluntary contractions in the antagonist muscle groups. The smaller amplitude of the EMG signal during PNES could be explained by submaximal muscle activation. This could mean that amplitude is a relatively weak parameter to differentiate PNES from simulated seizures (in cases where this is the diagnostic problem), whereas it clearly separates GTCS from PNES.

Two EMG parameters distinguished between the PNES and GTCS at a group level, but with considerable overlap at the individual level. The duration of the muscle activation, as shown by the EMG recordings was longer in the PNES

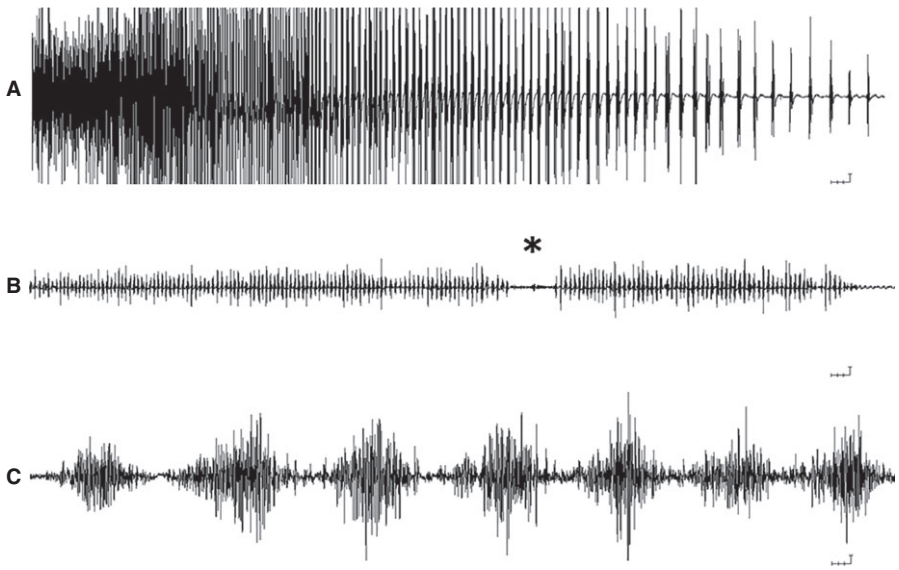

Figure 3.
The clonic phase. (**A**) The end of the tonic phase and the whole clonic phase of a GTCS. Please notice the longer and longer silent periods interrupting the tonic EMG discharges. (**B**) The clonic phase of a case of PNES. Observe that the silent periods have approximately similar duration throughout the episode. After a short pause (asterisk) the cloni start again. (**C**) In this case of PNES the clonic phase is not separated from the tonic phase; there are no silent periods. The amplitude of the EMG discharges is waxing and waning throughout the episode.
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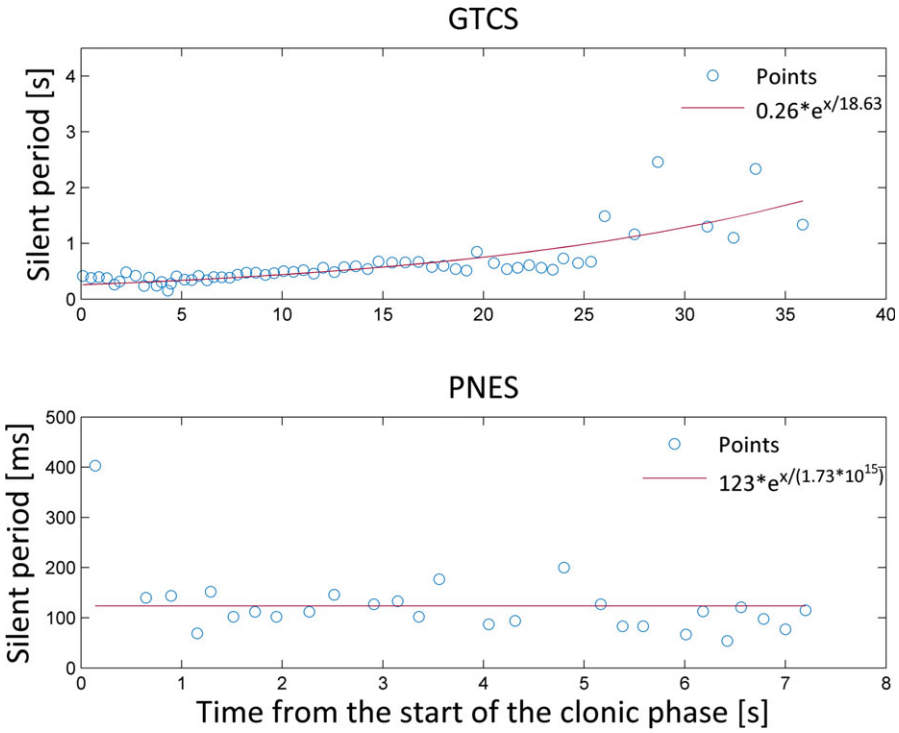

Figure 4.
The dynamics of the silent period (SP). (**A**) In GTCS the duration of the SPs increases exponentially (red line) toward the end of the seizure. (**B**) In PNES the duration of the SPs does not increase exponentially.
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group than in the GTCS. However, the duration of 7 of 18 PNES episodes fell within the range of the GTCS. The clonic phase was clearly distinguished from the tonic phase in the EMG recordings of all GTCS. However, this was possible in only 11 of the 18 episodes of PNES. Despite providing insight into the mechanism of muscle activation during convulsive PNES, these findings are not helpful for clinical differential diagnosis, due to the overlap at individual level.

However, no less than three EMG parameters differentiated between PNES and GTCS also at the individual level: the RMS of the amplitude, dynamics of the HF/LF ratio, and the dynamics of the SPs. A combination of HF/LF ratio and RMS yielded a separation boundary that completely distinguished all PNES from the GTCS. A blinded review of the EMG signals and derived quantitative parameters accurately separated between the tonic muscle activation of the GTCS and the PNES in 97.2% of the cases. Assessment of SP dynamics during the clonic phase (when present) increased the accuracy to 100%. Assessment of the EMG signals could distinguish between GTCS and convulsive PNES, even when both types of episodes occurred in the same patient.

The prerequisite for adequate management of patients with PNES is a correct diagnosis.[13] Misdiagnosis of PNES leads to wrong therapeutic choices (antiepileptic drugs), unnecessarily exposing the patients to side effects and imposing unnecessary costs to the health care system.[14,15] The gold standard for diagnosing PNES is video-EEG. However, this is resource demanding and not available everywhere. In some individuals, even video-EEG does not determine the diagnosis. A recently published task-force report suggested several levels of diagnostic certainty based on the available data.[1] Several neurophysiologic, neurohumoral, and neuropsychological tests could be used as adjunctive parameters to increase the diagnostic certainty. Analysis of heart rate variability accurately differentiated between complex partial seizures and PNES, with a sensitivity of 73–88%.[8] The absence of postictal rise in the serum prolactin level has a mean sensitivity of 89% for PNES.[3,16] However, this requires an early postictal blood sample, which usually is only available during an in-patient setting. Time-frequency mapping of the rhythmic limb movements recorded with a wrist-worn accelerometer allowed differentiation between epileptic and nonepileptic, psychogenic convulsive events, with a sensitivity of 75–92.7%.[9] This is based on the characteristic pattern of rhythmic movements during PNES. However, not all cases of convulsive PNES have alternating movements. In our series only 7 of the 18 episodes of PNES included a clonic phase. Analysis of the surface EMG recordings allowed an accurate differentiation between epileptic and nonepileptic convulsive seizures, also when a clonic phase was not present.

Although our results clearly differentiated between simulated seizures and the other two conditions, one has to be cautious with interpreting this, as the parameters of the simulated seizures largely depend on the received instructions. The duration of the simulated seizure was clearly determined by the instruction. The healthy controls were instructed to do maximal voluntary contraction during the simulated tonic phase. This could explain the higher RMS during the simulated seizures as compared with PNES. However, the HF/LF ratio was smaller for simulated seizures than PNES, and the dynamics of the HF/LF and the dynamics of the clonic phase also distinguished between the simulated seizures and the GTCS. These data suggest that the mechanism of muscle activation is different in the three studied conditions: volitional activation, PNES, and epileptic seizures.

A systematic analysis of other pseudo-seizure types was beyond the scope and limitations of this study. However, it is highly probable that surface EMG recordings will prove to be useful in those conditions too. Supporting document 1 shows the recordings during a convulsive syncope. The quantitative analysis of the surface EMG signals clearly distinguishes it both from PNES and from GTCS. Additional studies specifically addressing this issue are needed to elucidate this.

Although video-EEG monitoring is considered the gold standard for diagnosing PNES, it is less than perfect.[17] The differences in the onset of tonic contraction and the gradual change in the rhythm of the clonic phase of the GTCS may often already be apparent to the eye of the observer. This, however, requires both considerable experience and the possibility to see the seizures, either directly or on a good video recording. Our quantitative method is independent of visual inspection and provides an objective measure and documentation that allow reliable distinction also with less experience.

Portable devices can record and analyze surface EMG signals in an ambulatory setting.[18] This study suggests that surface EMG may carry a potential for electrophysiologic biomarker: Implementing automated detection algorithms based on these EMG features, alone or in combination with accelerometer data[9,19,20] could provide valuable information for differentiating between epileptic and nonepileptic convulsive seizures, particularly if there was a caregiver who could give a description of the recorded event.

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Disclosure or Conflict of Interest

Author IC is currently employed by IctalCare A/S. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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