Interictal Epileptiform Discharges Do Not Change before Seizures during Sleep

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Summary: Purpose: Whether interictal epileptiform discharges (IEDs) increase, decrease, or are unchanged before epileptic seizures has implications for the pathophysiology of epilepsy. Prior studies relating IEDs and seizures have not demonstrated a change in IEDs before seizures. However, they have not controlled for changes in the depth of sleep. Our objective was to test the hypothesis that IEDs are related to seizures during sleep while adjusting for log delta power (LDP), a continuous measure of sleep depth.

Methods: Twenty-two seizures during sleep were identified in 16 subjects with epilepsy admitted for presurgical monitoring. The IEDs that occurred in the hour of sleep before each seizure were used to test the relation between IEDs and seizure occurrence. Sleep depth was measured by LDP (quantity of 1- to 4-Hz activity in 30-s epochs), and records were scored visually for sleep staging and for IEDs. Multivariate logistic regression analyses were applied.

Results: Adjusting for LDP, number of seizures before the current seizure, quartile of the night, and total number of IEDs that occurred during the night, IED did not increase or decrease before seizures (p > 0.1). The rate of IEDs increased directly with LDP (p = 0.0001), as shown in prior work.

Conclusions: IEDs are not activated or suppressed before seizures during sleep, suggesting that different pathophysiologic processes underlie these two phenomena. These results corroborate prior studies, while providing a more advanced analysis by adjusting for sleep depth and applying multivariate logistic regression analyses.

Key Words: Epilepsy—Seizure—Interictal epileptiform discharges—Sleep—Statistics.
METHODS

Subjects and seizures

The records of all adult epilepsy patients admitted for presurgical monitoring at the University of Michigan Epilepsy Laboratory between July 1998 and June 2000 were reviewed to identify seizures that occurred during sleep. Subjects ranged in age from 19 to 53 years (mean ± SD = 39.4 ± 9.7 years) and consisted of nine men and seven women. All had complex partial seizures with or without secondary generalization, and the majority (11 of 16; 69%) had partial seizures of temporal lobe origin. Five subjects had possible extratemporal lobe seizures.

Video-EEG polysomnography

All subjects underwent continuous digital video-EEG monitoring (Telefactor Corporation, West Conshohocken, PA, U.S.A.) as part of their epilepsy surgery evaluation. The standard 10-20 system (11) was implemented along with sphenoidal electrodes. Electro-oculogram (EOG) and chin electromyogram (EMG) channels were included to score sleep stages. The EEG was digitized using 200 Hz, and filter settings were set at 0.3 and 70 Hz. All patients were observed over one night. Subjects were asked to sleep between 10 p.m. and 6 a.m.

Sleep scoring and calculation of log delta power

Each subject’s recording was partitioned into display epochs of 30 s each for the purpose of sleep scoring. Visual scoring was performed with a modification of standard criteria (12). Because we did not have access to C3-A2, we used four channels, predominantly C3-O1 and C4-O2 with reference as needed to FP1-C3 and FP2-C4. All records were scored by M.L.M, a registered polysomnographic technologist. NREM stages 3 and 4 were combined into one stage. The data were reduced by eliminating alternate sample points, padded with 28 zeros on each side, and then multiplied by a Hanning window to obtain the Fast Fourier Transform (FFT) for 2-s segments. Half-overlapping windows were applied. The frequency resolution was 0.39 Hz. Delta power was calculated by summing the power in the delta frequency range, between the 0.79 and the 3.9 Hz bin. Delta power was then averaged over 30 s, and LDP was calculated by multiplying the log base 10 of the delta power by a factor of 10. Epochs of wake and artifact, detected by visual inspection, were excluded from the study.

 Determination of IEDs

Visual determination of IEDs within 20-s display epochs was performed after sleep staging was completed. The following reformatted montage was used for IED determination: Fp1-F7, F7-T3, T3-T5, T5-O1, Fp2-F8, F8-T4, T4-T6, T6-O2, C3-T3, T3-Sp1, Sp1-Sp2, Sp2-T4, T4-C4, FZ-CZ, CZ-PZ, F7-F3, F3-FZ, FZ-F4, and F4-F8. The inclusion criteria were adapted from those of Gloor (13) and included (a) restricted triangular transient clearly distinguishable from background activity, with the spike component having an amplitude of at least twice that of the preceding 5 s of background activity in any channel of EEG, (b) duration of ≥200 ms, and (c) presence of a field, as defined by involvement of a second adjacent electrode. Our rationale for including an amplitude criterion was to interpret IEDs conservatively and to exclude equivocal IEDs. Two authors (B.A.M. and M.L.M) independently performed visual detection on one NREM–REM cycle within each subject’s recording. In studies in which IEDs were detected by one author and not by another, the IEDs in question were reviewed, and a consensus reached about which events constituted IEDs. The remainder of the study was then reviewed for IEDs by B.A.M., who was blinded to the time when the seizure occurred. Data were analyzed to determine the relation of IEDs to seizures while adjusting for LDP. Many of our subjects had either unilateral IEDs or a small number of independent, bilateral IEDs. Therefore, to maximize our sample size, and therefore statistical power, we did not separate the various categories of IEDs (e.g., left temporal, right temporal).
Statistical analyses

The same 30-s epochs created for sleep scoring and LDP measurement were used for analysis. In only 5% of the data did instances occur of more than one IED within a single epoch. Therefore, it was determined that a binary indicator for IED occurrence (1, IED occurred; or 0, IED not occurred) in each 30-s epoch would be more suitable for analysis rather than a more complex indicator for multiple IEDs. For each subject, the quartile of the night that the seizure occurred (calculated from sleep onset to time of waking), the number of prior seizures that night, and the total number of IEDs the subject had during the night were determined.

These factors were included in the model to account for biologic differences between patients, and to adjust for their confounding influence on the occurrence of IEDs. Quartile of the night that the seizure occurred was included in the analysis to adjust for the domination of certain stages of sleep during the night, because these stages in and of themselves have relations to IED occurrence. Number of prior seizures was also included because prior seizure occurrence during the night could be correlated with subsequent seizures and thus have an effect on the occurrence of IEDs. Finally, the total number of IEDs that occurred during the night was considered because subjects had variable numbers of IEDs. Thus a subject who had 10 IEDs the hour before the seizure and had 20 total IEDs for the entire night would contribute different information to the analysis from that of a subject who also had 10 IEDs the hour before the seizure but had 100 total IEDs for the entire night. The former would imply increasing IEDs before the seizure, whereas the latter would imply that IEDs occurs evenly over the night regardless of when the seizure occurs.

All analyses were performed with the SAS statistical package (SAS Institute Inc, Carey, NC, U.S.A.). The study involved taking repeated measurements (e.g., IEDs and LDP) on the same subject over time. Such a design introduces correlations between observations within a cluster of observations from the same subject. If the analysis did not adjust for these correlations, our results would underestimate the standard error and would be more likely to give us falsely significant results. To analyze these data properly, a logistic regression was performed based on generalized estimating equations (GEEs) (14). The log odds of having an IED [log(probability of having an IED)/probability of not having an IED)] was modeled as a function of LDP, time, total number of IEDs in the night, quartile of the night of seizure occurrence, and the number of prior seizures. The method of GEEs requires a correlation matrix to be specified that explains the type of relation between IEDs within each seizure. In our analysis, an exchangeable correlation matrix was specified, which assumes that IEDs are equally correlated among each other within a seizure regardless of how close or far apart they are from each other. We explored other correlation matrices, and they showed similar results.

Stage of sleep presented another confounding influence on the occurrence of IEDs. Therefore this analysis was applied to all data as well as to two subsets of the data. One subset included only those observations that occurred during NREM sleep, excluding rapid eye movement (REM) sleep. The other subset consisted of 15 seizures, in 11 subjects, in which the hour before consisted of continuous NREM sleep. Stage of sleep was considered as a factor in this analysis because past studies have shown that NREM sleep activates IEDs, whereas REM sleep suppresses IEDs (15). Therefore, epochs of REM sleep would provide little information for analysis of IED occurrence because there is minimal IED activity in these periods. To account for differences in IED activity between REM and NREM sleep, the GEE model was applied to the two subsets of data to see whether the results still held during NREM sleep epochs.

We determined whether differences in gender, age, seizure type (e.g., partial vs. secondarily generalized), and sleep deprivation affected the relation between IEDs and seizures by using the $\chi^2$ test for categorical variables and an independent samples $t$ test for continuous variables. For all statistical tests, the level of significance was set at $\alpha = 0.05$.

RESULTS

Twenty-two seizures occurred in 16 subjects. Seven seizures occurred in quartile 1, four in quartile 2, three in quartile 3, and eight in quartile 4. Of the 22 seizures studied, 13 occurred in subjects who had no prior seizures during the study, four occurred in subjects who had one prior seizure, three occurred in subjects who had two prior seizures, and two occurred in subjects who had three prior seizures. Total number of IEDs ranged from 9 to 1,697 (mean ± SD = 234 ± 419.5). Number of IEDs in the preictal period ranged from 2 to 115 (mean ± SD = 27.1 ± 27.7). Only two subjects had preictal periods containing two IEDs. Nineteen of 22 seizures were partial complex seizures, and three seizures were secondarily generalized. These three seizures occurred in three subjects. Fourteen seizures occurred in the temporal lobe, and eight seizures, occurring in five subjects, had possible extratemporal origins. Finally, six of 16 subjects were sleep deprived; these six subjects contributed 10 seizures (occurring during sleep on non–sleep-deprived nights) to the study.

The GEE model, using all of the data and adjusting for prior seizures, quartile of the night, and total number of IEDs, found no relation between seizure and IED occurrence ($p > 0.01$). LDP, however, was associated with a higher probability of IED occurrence ($p = 0.03$) as...
shown in previous work (5,6). The parameter estimate for LDP indicates that for a 5-unit microvolt increase in LDP, the odds of having an IED is 1.5 times as likely. The analysis also showed that studies having a higher total number of IEDs were associated with a higher chance of IED occurrence (p = 0.0001). No other factors in the model were related to IED occurrence. Figure 1A and B illustrate the relation of IEDs to seizures in two separate subjects.

Similar results were seen using the subset of data limited to epochs occurring during NREM sleep, excluding REM sleep epochs. No relation was found between IED occurrence and seizures (p > 0.01). The GEE analysis showed that LDP had a significant relation to IED occurrence (p < 0.0001). The coefficient of LDP indicated that for a 5-microvolt increase in LDP, there was a 2.2 times increase in the probability of IED occurrence. Also concurring with these results, total number of IEDs was significantly related to seizure occurrence (p < 0.0001).

Finally, the subset of 15 seizures in 11 subjects with continuous NREM sleep with no wakefulness for the entire hour before the seizure was used to carry out the GEE model. Similar results were found. Seizures were not significantly related to IED occurrence (p > 0.01), whereas LDP and total number of IEDs were significantly related to IED occurrence (p = 0.01 and 0.02, respectively). The analysis showed that the odds of IED occurrence increased by 2.0 times with a 5-microvolt

![Figure 1](https://example.com/figure1.png)

**FIG. 1.** Relation of epileptiform discharges (IEDs) to log delta power (LDP) during sleep in two subjects (A, B). Each diamond represents one IED. Each point on the graph represents the average LDP over a 5-min period. Graphs encompass the hour of sleep before a seizure. Spikes clearly increase with LDP, but do not increase or decrease as the seizure event nears.
increase in LDP. Total number of IEDs also was significantly related to seizure occurrence (p < 0.0001).

Age, gender, seizure type (partial vs. generalized), seizure localization (temporal vs. extratemporal), and sleep deprivation did not influence our results. The GEE models were applied to subsets of seizures: complex partial seizures, seizures occurring in sleep-deprived patients, and possible extratemporal seizures. All analyses con-
curred with our overall results; however, the subset in-
volving possible extratemporal seizures was too small to estimate the GEE parameters correctly, and therefore re-
sults could not be confirmed in this subset.

Further analyses were performed to test the hypoth-
eses that (a) seizures are related to IEDs even when LDP
is excluded from the model, and (b) seizures are related
to LDP. GEE models excluding LDP still showed no
relation between seizures and IEDs. A linear mixed
model showed no relation between LDP and seizures.

DISCUSSION

Our data showed no change in the probability of IED
occurrence in the period before seizures during sleep,
even after accounting for LDP. Our findings also showed
that the probability of IED occurrence increased as LDP
increased. An increased number of total IEDs also led to
significant increases in the probability of IED occur-
rence.

To analyze these data and types of variables, we used
a logistic regression model based on the method of GEEs
to look for a relation between IED occurrence and sei-
zure. Such a method enables us to analyze continuous
data, and it also is robust to missing data (i.e., as occurred
in those epochs with wake or artifact). Because the data
involve measurements from the same subject, correla-
tions between observations also can be handled by a
GEE model. Our analysis therefore, provides a more
thorough approach to answering the question of whether
seizures are related to IED occurrence. Our analysis ad-
justs for differences in sleep depth, which have been
shown to have a significant impact on the probability of
IED occurrence. We also looked at differences in IEDs
across a continuum of time and not in predefined inter-
vals. Quartile of the night, prior seizures, and total num-
ber of IEDs during the night also were accounted for.

These observations are consistent with earlier findings
of no change in the rate of IEDs before seizures (2–4).
These important studies laid the foundation for the work
presented here. Our data provide confirmation of these
studies by using statistical analyses that adjust for sleep
depth and other variables, and by using visual IED con-
firmation as opposed to automated IED detection with
visual confirmation. Although the automated approach
with visual confirmation eliminates false-positive IEDs,
it may miss true-positive IEDs not detected by the auto-
matic IED program. We also were able to control for
state of arousal by using LDP, a continuous measure of
sleep depth. Use of continuous measure of the depth of
sleep is advantageous over use of categorical states of
arousal (e.g., NREM stages 1, 2, 3, 4, and stage REM),
which result in loss of information.

Our data do not support that IEDs facilitate or inhibit
seizures during sleep. The lack of a temporal relation
between IEDs and seizures is intriguing, as both events
are activated by NREM sleep and suppressed by REM
sleep (15). However, whereas IEDs are activated by in-
creases in sleep depth (6), seizures appear to be more
common in lighter sleep stages (16–18). Additionally,
we did not find a relation between LDP and seizures.
This discrepancy suggests that different pathophysi-
ologic processes underlie the two phenomena. Steriade et
al. (19) postulated that progressive hyperpolarization
within thalamocortical projection neurons predisposes to
epileptic activity during sleep. The IEDs and seizures
may be preferentially activated by different levels of hy-
perpolarization within these thalamocortical projection
neurons. An alternative explanation is that epileptic sei-
zures may be facilitated by state transitions, which
result in changes in the levels of hyperpolarization within
thalamocortical projection neurons. This model may ex-
plain why pathophysiologic processes such as obstruc-
tive sleep apnea, which fragment sleep, have been
associated with worsening seizure control, and why treat-
ment of these disorders may improve seizure control
(20–22).

One of the limitations of our study is that we used
surface EEG recordings. As compared with intracranial
recordings, surface EEGs may miss interictal activity and
also may contain more artifacts. Because many of our
subjects had either unilateral IEDs or a small number of
independent, bilateral IEDs, we were not able to separate
out various categories of IEDs (e.g., left temporal, right
temporal). Follow-up studies with larger numbers of pa-
tients and intracranial recordings may be useful in study-
ing whether the focality of IEDs preceding a seizure is
influenced by seizure onset.

In conclusion, our findings support those of other stud-
ies that have reported no change in the rate of interictal
spiking before seizures. Our analysis also supports pre-
vious work showing that deeper levels of sleep are
associated with increased IED occurrence. Further
experimental and clinical studies will be needed to un-
ravel the pathophysiologic relation of IEDs to seizures.

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REFERENCES
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