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Ryan Miller

Cooper Medical School of Rowan University

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Ryan Miller, Class of 2018

Dr. Evren Burakgazi-Dalkilic , MD, Department of Neurology

Utility of interictal EEG in determining epilepsy severity

Clinical Research Project - Scholar's Workshop

Abstract:

Objectives

EEGs are used to detect interictal discharges (IEDs) in patients with a known history of epilepsy, but there is unclear evidence in regards to the utility of this information. There is contradicting information in regards to whether the presence of and frequency of these IEDs can predict measures of epilepsy severity, possibly due to subject selection and recording modalities. In an effort to increase generalizability, we studied a population with very little exclusion criteria using routine EEGs, a technique used most commonly in clinical practice. We predicted that there would be an association between seizure frequency and the detection and/or frequency of IEDs. We also predicted that there would be an association between anti-epileptic drug (AED) usage and the detection and/or frequency of IEDs.

Methods

We analyzed the EEGs and clinical records of 920 patients from the Cooper University Health Care Neurology outpatient clinic. Patients, ages 18 and over, who presented for outpatient routine EEG recording between January 2015 and June 2017 were included in this study. A total of 144 patients with a history of at least two unprovoked seizures were included in our analyses.

Results

We did not find an association between seizure frequency and the presence of and/or frequency of IEDs. Anti-epileptic drug use was not associated with the presence of and/or frequency of IEDs. Other characteristics, such as epilepsy duration, age at the time of EEG, and time from most recent seizure, had no association with the presence of and/or frequency of IEDs.

Conclusions

In our study population, interictal EEG did not serve any utility in determining epilepsy severity. These results are similar to one other study that focused on a general patient population like ours. However, our study differs from others which focused on more specific subject populations. As a result, clinicians should take into account the patient's age, particular epilepsy syndrome, and EEG recording modality when determining the utility of IEDs.

Introduction:

In patients with a known diagnosis of epilepsy, interictal epileptiform discharges (IEDs) are pathological patterns of brain activity on EEG that occur between seizure events (1). While seizures, or ictal discharges, represent the primary event for the epilepsy patient, IEDs offer clinicians a source of information that is less labor intensive and time consuming to retrieve. For example, the detection of IEDs in itself can confirm a diagnosis of epilepsy (2). In addition, the features of these IEDs, such as their location and appearance, can help clinicians determine an epileptogenic focus in the brain or diagnose a specific epilepsy syndrome (2). Routine EEGs in patients with epilepsy are common in clinical practice, but it is not always clear how to use this information, especially as it pertains to IEDs.

There has been discrepancy in the literature in regards to whether the presence and frequency of IEDs bears any weight on epilepsy severity. In 1970, Ajmone Marsan and Zivin found that a younger age at the time of EEG, a recent seizure within 7 days, and a seizure frequency of greater than 1 per day were all associated with the presence of or a higher frequency of IEDs (3). They also observed a relationship

between anti-epileptic drugs (AEDs) and IEDs, in which there were fewer IEDs off AEDs (3). This study was based on serial routine EEGs in elderly patients with focal or generalized epilepsy (3). In 1988, Desai et al. found that an epilepsy duration of greater than 10 years and the use of greater than 1 AED were both associated with the presence of or a higher frequency of IEDs (4). However, they found no association between seizure frequency and the presence of or a higher frequency of IEDs (4). This study was based on a single routine EEG in adult chronic epilepsy patients with focal or generalized seizures (4). In 1990, Sundaram et al. found that a recent seizure within 2 days and a seizure frequency of greater than 1 per month were both associated with the presence of or a higher frequency of IEDs (5). However, they found no association between the age at the time of EEG and the presence of or a higher frequency of IEDs (5). They also found no association between the use of AEDs and the presence of or a higher frequency of IEDs (5). This study was based on a single routine EEG in adult epilepsy patients with focal or generalized seizures (5). In 1998, Drury and Beydoun found that having greater than 1 seizure per month was associated with the presence of or a higher frequency of IEDs (6). However, they found no association between epilepsy duration, age at the time of EEG, and use of AEDs with the presence of or a higher frequency of IEDs (6). This study was based on a single routine EEG in elderly patients with focal or generalized epilepsy (6). In 2005, Janszky et al. found that an increased epilepsy duration and a seizure frequency of greater than 1 per month were both associated with the presence of or a higher frequency of IEDs (7). However, they found no association between age at the time of EEG and use of AEDs with the presence of or a higher frequency of IEDs (7). This study was based on long term monitoring in patients with medically refractory temporal complex partial seizures (7). In 2008, Krendl et al. found that a seizure frequency of greater than 1 per week was associated with the presence of or a higher frequency of IEDs (8). This study was based on long term monitoring in patients with medically refractory temporal complex partial seizures (8). Most recently, in 2011, Selvitelli et al. found that no association existed between epilepsy duration, age at the time of EEG, recent seizure, seizure frequency, and use of AEDs with the presence of or a higher frequency of IEDs (9). This study was based on a single routine EEG in an adult population with a history of 2 or greater presumed focal-onset seizures (9). Part of the reason for this discrepancy is that fact that the populations in each of these studies were different. The methodology for collecting data about the IED presence and frequency was also variable between studies. In practice,

neurologists and other clinicians often adjust or modify AEDs with the goal of suppressing IEDs to prevent further epileptic seizures, but it is unclear if this approach is effective given the mixed results from these prior studies.

Due to a lot of this contradicting information, we sought to investigate the utility of interictal EEG in adult patients with established epilepsy, regardless of type and age, in an effort to increase our generalizability. Since many studies may show differences in results because of the methods by which IEDs are detected and the types of epilepsy patients being studied, we chose a population with very little exclusion criteria. We also used data from routine EEGs because this is the most common modality for collecting information in the clinic, and thus the results from this study will pertain to the majority of patients. We predict that there will be an association between increased seizure frequency and the presence of or a higher frequency of IEDs. We also predict that there will be an association between increased AED drug usage and a lack of IED detection or a lower frequency of IEDs.

Methods:

Subjects

All outpatients presenting for routine EEG at the Cooper University Health Care Neurology outpatient clinic in Cherry Hill, NJ between January 2015 to June 2017 were obtained from medical informatics and considered for the study. The inclusion criteria consisted of at least two unprovoked seizures, as well as an age of greater than 18. The exclusion criteria consisted of an age of less than 18, a provoked or acute seizure, a history of substance or alcohol abuse, and a non-seizure diagnosis (such as psychogenic non-epileptiform seizures) at any time. 920 patients presented to the EEG laboratory during this time frame, and of this cohort, 144 met the inclusion criteria for our study.

EEG recording

Digital EEGs were performed in the lab at the Cooper University Health Care Neurology outpatient clinic in Cherry Hill, NJ using the standard 10/20-electrode placement system and one channel of EKG monitoring. A minimum of 3 montages were reviewed. Technical standards were in accordance with the American Clinical Neurophysiology Society. EEG recordings varied from 20 to 60 minutes. Activating techniques, including hyperventilation and intermittent photic stimulation, were used unless there was a contraindication.

Medical record analysis of seizure history and IED presence/frequency

Through chart review, the patients' most recent seizure from the time of the routine EEG recording (in days), their duration of epilepsy (in years), their age at the time of the EEG recording (in years), and their seizure frequency (number per year) were all determined. The usage of anti-seizure medication at the time of the routine EEG was also determined for each patient. Chart review of the patients' routine EEG results were examined and categorized by whether IEDs were identified (n=32) or not (n=112) during the recording. IEDs were defined as spike or sharp wave discharges that clearly stood out from the background rhythms, with or without an aftergoing slow wave. IED frequency was calculated by counting the total number of IEDs seen in the routine EEG study and dividing by study duration.

Statistical analysis

Since the data was not normally distributed, the Mann Whitney U test was used to compare the group with IEDs on routine EEG (n=32) and the group without IEDs on routine EEG (n=112) on the following variables: age at the time of EEG (in years), epilepsy duration (in year), time since last seizure (in days), and seizure frequency (in number per year). A two-tailed test and a significance level of $\alpha = 0.05$ were used. Spearman's correlation analyses were conducted on the group who had EEGs showing IEDs to see if any relationships existed between the same aforementioned variables. Within the group with IEDs on EEG, the frequency of these IEDs was compared between subjects taking AEDs at the time of study (n=18) and those who were not (n=14). This comparison was analyzed using the Mann Whitney U test. In

addition, patients with IEDs on EEG were stratified into high and low frequency depending on whether they were at or above the median (high frequency) or below the median (low frequency). They were compared on the same aforementioned variables using the Mann Whitney U (time since last seizure, epilepsy duration, and seizure frequency) and two-sample Student t-test (age at the time of EEG).

Results:

Subject Characteristics

There were 920 patients who presented to the Cooper University Health System Neurology outpatient office in Cherry Hill, NJ for routine EEG between January 2015 and June 2017. Of this group, 144 patients met the inclusion criteria for the study. 76 females and 68 males made up this group. The mean age was 46.47 years, the range was 18 to 82 years, and the median was 46 years. The mean for duration of epilepsy was 21.89 years, the range was 1 to 50 years, and the median was 20 years. The mean for seizure frequency per year was 4.64 events, the range was 1-36 events, and the median was 3 events. The mean for time since last seizure was 360.90 days, the range was 2 to 4624 days, and the median was 110.50 days. 32 out of the 144 patients had IEDs detected on routine EEG (22.22%) and 112 did not (77.73%). Of the group with IEDs, the mean for frequency was 11.56 per hour, the range was 1 to 42 per hour, and the median was 10 per hour. 18 patients who had IEDs detected on routine EEG were using AEDs at the time of study (56.25%) and 14 were not using AEDs at the time of study (43.75%).

IED presence and clinical epilepsy severity

When comparing the IED positive group with the IED negative group, no statistically significant differences were detected when examining the elapsed time since the most recent seizure (Mann-Whitney U statistic = 1586.50, $Z = -0.99$, $p = 0.32$), seizure frequency (Mann-Whitney U statistic = 1611.50, $Z = 0.86$, $p = 0.39$), epilepsy duration (Mann-Whitney U statistic = 1664.50, $Z = -0.61$, $p = 0.54$), and age at the time of EEG (Mann-Whitney U statistic = 1725.50, $Z = -0.32$, $p = 0.75$) (**Table 1**).

IED frequency and clinical epilepsy severity

Among those patients with IEDs, a Spearman correlation matrix was used to assess for any relationships among the variables of IED frequency, days since last seizure, seizure frequency, epilepsy duration, and age at the time of EEG (**Table 2**). The only significant associations existed between days since last seizure and seizure frequency ($r = -0.66$, $p = 0.0004$), as well as epilepsy duration and age at the time of EEG ($r = 0.96$, $p = 0$). All other associations were statistically insignificant. There was no significant difference between the subjects with high IED frequency, or those at or above the median, and those with low IED frequency, or those below the median, with regard to days since last seizure (Mann-Whitney U statistic = 120, $Z = -0.28$, $p = 0.78$), seizure frequency per year (Mann-Whitney U statistic = 109, $Z = 0.70$, $p = 0.48$), epilepsy duration (Mann-Whitney U statistic = 92.50, $Z = 1.32$, $p = 0.19$), and age at the time of EEG ($t = 1.30$, $p = 0.20$) (**Table 3**). In addition, there was no statistically significant difference between the IED frequency and AED usage ($U = 123.50$, $Z = 0.08$, $p = 0.94$).

Discussion:

In a general population of adult patients who experienced at least two unprovoked seizures and who presented at an outpatient neurology clinic for routine EEG, we have shown that the presence of IEDs had no relationship with the measures of epilepsy severity, namely seizure frequency, time since the most recent seizure, epilepsy duration, and age at the time of EEG. In addition, the frequency of IEDs had no relationship with these same measures. There was also no association between AED usage and IED frequency.

Several past studies detected an association between IED frequency and seizure frequency, but these were conducted on specific epilepsy subpopulations and used differing EEG recording modalities. Janszky et al. and Krendl et al. both detected an association between IED frequency and seizure frequency in patients with medically refractory temporal complex partial seizures (7, 8). This association was seen in patients

who had more than one seizure per week, however both research groups used the video EEG monitoring modality (7, 8). Drury and Beydoun saw an association between increased IED frequency and a seizure frequency of greater than one per month, but this was in a patient group older than 65 years (6). Sundaram et al. led a study, which was similar to ours in terms of EEG recording modality and subject population, and did find an association between increased IED frequency and a seizure frequency of greater than one per month (5). Other studies with similar methodology, which were led by Desai et al. and Selvitelli et al., yielded similar a similar result to ours, in that no association was detected (4, 9). These discrepancies are most likely due to the patient population under study. In addition, our study population had an average seizure frequency that was far less than prior studies which did detect a difference.

In regards to the time since most recent seizure, other studies found associations. Namely, Sundaram et al. found an increased incidence of IEDs when an EEG was conducted within 2 days of a seizure event (5). Ajmone Marsan and Zivin also found a similar association but within 7 days of a seizure event (3). Selvitelli et al. found no association, however, which coincides with the results of this study (9). Since our study was conducted in an outpatient clinic, in which most patients are being monitored at length and have been seizure-free for a sizable timespan due to AED usage, we are likely not finding a statistically significant association.

The only prior study which showed an association between age at the time of EEG and IED presence and frequency was conducted by Ajmone Marsan and Zivin (3). They found that as age at the time of EEG increased, there was an association with fewer IEDs detected. Other studies, however, such as Drury et al., Sundaram et al., Janszky et al, and Selvitelli et al., found no association, similar to ours (5, 6, 7, 9). An increased epilepsy duration was associated with an increased IED frequency in the study by Janszky et al., but they only studied patients with medically refractory temporal complex partial seizures (7). Desai et al. found an association between greater than 10 years of epilepsy duration and increased IED frequency, but only patients with generalized seizures were used in their analyses (4). The only result similar to ours in terms of epilepsy duration and IED presence and frequency was Selvitelli et al., which showed no association (9). They, too, used a sample population with very little exclusion criteria. The fact that

heterogenous cohorts and differing EEG recording modalities are being used in these studies is the likely reason for these mixed findings.

Fewer IEDs were detected off of AEDs in a study conducted by Ajmone Marsan and Zivin (3). Desai et al. found an association between increased IEDs and taking more than one AED (4). Other studies, however, conducted by Selvitelli et al., Sundaram et al., and Drury and Beydoun, found no association between these two measures, similar to our results (5, 6, 9).

Our study had several limitations. First, all of our data was collected using chart review. Many of the physician notes did not contain all of the pertinent info being used in this study. For example, some of the data, including time since most recent seizure event, was calculated for some patients by looking further back in the chart for emergency department visits or notes from outside departments and institutions. In addition, our study was conducted using the patient records from one outpatient clinic site. Many of these patients are well controlled on their AED regimens and thus the association between IEDs and measures of epilepsy severity may be underrepresented as a result. Inpatient EEG was not captured in this outpatient-focused study, which certainly alters the patient population and limits the results we found. Lastly, some of the patients had several routine EEG recordings collected during the span of their disease. Since we only had access to the records of these patients during the time frame described above, we were only able to assess for relationships at this interval and might have missed associations at earlier time points.

Conclusions:

Based on the results of our study, coupled with the findings from earlier studies, it is essential for clinicians to account for the particulars of a patient's situation when determining the utility of their EEG findings. Age, type of EEG modality, and specific epilepsy syndrome should all be accounted for when making decisions based on a patient's EEG, especially when that EEG shows evidence of IEDs. In our study, we showed that there was no association between IED presence and frequency with measures of

epilepsy severity, and therefore in a general adult patient undergoing routine EEG, IEDs don't offer any meaningful clinical information. However, other studies which focused on a more specific subpopulation did show utility to IEDs. Further studies need to delineate these differences by targeting additional subpopulations. It is clear that IEDs do offer information based on prior studies but sampling the general adult population may not be the best solution. Epilepsy etiology could also factor into the equation and should be studied in the future. For example, it could be possible that etiology, such as trauma or malignancy, bears weight on the presence and frequency of IEDs. Clinicians need to study these associations before determining how best to use this information in guiding patient management.

	IEDs present on EEG (n=32)	IEDs not present on EEG (n=112)	Statistical comparison
Elapsed time since most recent seizure (in days)	Mean 426.72, range 4 to 4624, median 132	Mean 342.10, range 2 to 3692, median 106	U = 1586.50, Z = -0.99, p = 0.32
Seizure frequency (in events per year)	Mean 4.06, range 1 to 36, median 3	Mean 4.80, range 1 to 24, median 3	U = 1611.50, Z = 0.86, p = 0.39
Duration of epilepsy (in years)	Mean 23.09, range 1 to 42, median 20	Mean 21.54, range 1 to 50, median 19.50	U = 1664.50, Z = -0.61, p = 0.54
Age at time of EEG (in years)	Mean 47.50, range 22 to 81, median 47	Mean 46.18, range 18 to 82, median 46	U = 1725.5, Z = -0.32, p = 0.75

Table 1: Measures of epilepsy severity between subjects with and without IEDs on routine EEG.

	IED frequency (number of IEDs/time)	Elapsed time since most recent seizure (in days)	Seizure frequency (in events per year)	Duration of epilepsy (in years)	Age at time of EEG (in years)
IED frequency (number of IEDs/time)	R = 1				
Elapsed time since most recent seizure (in days)	R = -0.29, p = 0.11	R = 1			
Seizure frequency (in events per year)	R = 0.20, p = 0.27	R = -0.66, p = 0.00004	R = 1		
Duration of epilepsy (in years)	R = 0.28, p = 0.13	R = 0.31, p = 0.08	R = 0.17, p = 0.36	R = 1	
Age at time of EEG (in years)	R = 0.24, p = 0.19	R = -0.20, p = 0.26	R = 0.11, p = 0.53	R = 0.96, p = 0	R = 1

Table 2: Relationships between IED frequency and epilepsy severity measures using a Spearman correlation matrix.

	Elapsed time since most recent seizure (in days)	Seizure frequency (in events per year)	Duration of epilepsy (in years)	Age at time of EEG (in years)
High IED frequency (n=16)	Mean 461.81, range 4 to 4624, median 135.50	Mean 5.44, range 1 to 36, median 3	Mean 26.69, range 2 to 42, median 30.50	Mean 51.69, range 22 to 81, median 58.50
Low IED frequency (n=16)	Mean 391.63, range 72 to 2652, median 122	Mean 2.69, range 1 to 7, median 2.5	Mean 19.50, range 1 to 42, median 18.50	Mean 43.31, range 23 to 74, median 42
Statistical comparison	U = 120, Z = -0.28, p = 0.78	U = 109, Z = 0.70, p = 0.48	U = 92.50, Z = 1.32, p = 0.19	T = 1.30, p = 0.20

Table 3: Measures of epilepsy severity between subjects with high and low IED frequency on routine EEG.

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