Original article

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Prolonged EEGs in adult patients with a first unprovoked seizure: a prospective pilot study

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ABSTRACT – *Aims.* Definitions of epilepsy have changed to include a first unprovoked seizure with a high (>60%) risk of recurrence in the next 10 years. A single seizure and an epileptiform discharge on an EEG would suffice for this diagnosis. We hypothesized that an extended six-hour EEG in adult patients presenting with a first unprovoked seizure would demonstrate an increased yield of epileptiform discharges in comparison to a standard 30-minute EEG, and therefore higher rates of epilepsy diagnosis.
Methods. Thirty-eight patients were recruited at Hamilton Health Sciences over six years and 36 underwent extended six-hour EEGs.
Results. Two of seven patients demonstrated epileptiform discharges on their EEG after only the first 30 minutes of recording, observed during sleep for both patients. This correlated to an overall increase of 5.56%, or a yield of 29%.
Conclusion. A third more patients could benefit from early diagnosis with extended EEGs. The rate of epilepsy diagnosis based on EEG overall was superior to that of brain imaging (19% *versus* 6%). Given the limitations due to sample size in this study, a larger trial would be beneficial to confirm these findings.

Key words: epilepsy diagnosis, extended EEG, first seizure, unprovoked seizure, adult

With recent changes to the definition of epilepsy from only at least two recurrent unprovoked seizures to including an unprovoked seizure and a high (>60%) risk of recurrence over the next 10 years or the diagnosis of an epilepsy syndrome (Fisher *et al*., 2014), more emphasis is placed on risk recurrence after a first seizure for the diagnosis of epilepsy. The American Academy of Neurology guidelines on management of an unprovoked first seizure in adults (Krumholz *et al*., 2015) makes it clear that an epileptiform discharge on EEG puts patients at a high risk of recurrence. If EEG can thus be used to make a diagnosis of epilepsy before the patient has a second seizure, early treatment may greatly improve short-term outcomes for patients (Marson *et al*., 2006).

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Many aspects of EEG have already been studied to determine their relationship to demonstrating epileptiform discharge. These include sleep (Veldhuizen *et al*., 1983), timing relative to the seizure (King *et al*., 1998), and the concurrent use of some anti-epileptic medications (Bruni *et al*., 1980; Duncan, 1987). However, length of the EEG has not been well studied in this patient population. Burkholder *et al*. (2016) have shown that in 4.5% of their outpatient EEGs, with an average duration of 59.4 minutes, interictal epileptiform activity was only seen after the first 30 minutes of recording. This correlated to an increased yield of 19%. Losey and Uber-Zak (2008) looked at longer EEGs (mean duration: 187 minutes) and found that in 47% of cases, the time taken to record the first interictal epileptiform discharge was longer than 20 minutes.

The purpose of the current study was to perform prolonged six-hour EEGs in adult patients with a first unprovoked seizure to determine if the longer studies improved the rates of early diagnosis of epilepsy.

Materials and methods

Patients were recruited at the Hamilton Health Sciences Center (Hamilton, Ontario, Canada) from March 2012 to February 2018. Patients aged 16 years or older were selected from epileptologists' clinics at Hamilton Health Sciences for eligibility in the study. All patients were deemed to have had a first unprovoked seizure and were excluded from the trial if a second seizure occurred prior to testing with EEG. Patients were not excluded from testing if they were taking anti-epileptic medication at the time of the EEG. Consent was obtained by a study coordinator and approval was given by the Hamilton Integrated Research Ethics Board. All patients had a six-hour continuous EEG with video recording. EEGs were obtained digitally through a 21-electrode array, arranged in the standard 10-20 system. EEG electrodes were connected to a 32-channel headbox by XLTEK (Oakville, Ont.) with low and high-frequency filter settings at 1 and 70 Hz. For most patients, hyperventilation and photic stimulation were performed. The EEGs were all interpreted at a single center by local electroencephalographers. Basic demographic data including type of first seizure, timing of EEG relative to first seizure, and number of patients recruited per year were recorded.

The first 30 minutes of the six-hour EEG was compared to the remainder of the study. Epileptogenic activity occurring after the first 30 minutes was considered to be significant, as this is the usual time frame for a routine EEG. Sleep on the EEG was documented, whether occurring during the first 30 minutes or during the remainder of the recording.

Results

Thirty-eight patients consented to the study. Median age at first seizure was 35 years. Two patients were not enrolled due to seizure recurrence prior to an extended EEG. The median (min, max) time to EEG was 62 days (29, 251). Twenty patients presented with either a generalized tonic-clonic or generalized tonic seizure. Fourteen patients presented with a focal seizure spreading to bilateral tonic-clonic movements, and two patients presented with a focal seizure only (*table 1*).

Twenty-four (67%) of the overall EEGs were entirely normal. Of the abnormal EEGs, three demonstrated only intermittent focal slowing, six demonstrated focal sharp waves or spikes, one demonstrated generalized spike-and-wave and polyspike-wave activity, and two had sharply contoured waves. In two of the seven studies with epileptogenic discharge, this was only seen after the first 30 minutes of recording. In both, the discharge occurred during sleep after five hours and one hour into the study, respectively. The median (min, max) time to EEG for the seven patients with epileptogenic discharge was 54 days (36, 104). In an additional four studies, the extended EEG also demonstrated new findings, which included slowing in the opposing hemisphere, more clear-cut epileptogenic discharge in two (seen in the sleep state in one patient), and a more generalized rather than focal appearance to the epileptiform discharge.

Only in one case was MRI clearly diagnostic in terms of epilepsy, demonstrating multiple foci of heterotopic grey matter along the margins of the lateral ventricles, minimally greater on the right. In one case, CT demonstrated a resolving hemorrhage, which was very likely the cause of seizure in that patient. In comparison with EEG, however, neuroimaging had a lower diagnostic yield.

Recurrence of seizure at one year was determined for all patients. In the group with 24 normal extended EEGs, five patents had seizure recurrence within a year and one patient within four years. Two patients remained on anti-epileptic drugs (AEDs), one due to the age of 91, and another due to abnormal MRI with multiple foci of heterotopic grey matter along the margins of the lateral ventricles. Neither of these patients had seizure recurrence at one year. Of the seven patients with epileptiform discharge on their extended EEGs, three had seizure recurrence within one year. Three of these patients remained on an AED due to the abnormal EEG without seizure recurrence at one year. Finally, of the five patients with abnormal extended EEGs without epileptiform discharge, two had seizure recurrence within one year.

Table 1. Clinical and EEG features of the patients.

Age	Gender	First seizure type	AED at time of EEG	Time to EEG (days)	EEG findings	Change in EEG after first 30 minutes?	Neuroimaging (MRI unless stated)	Seizure recurrence in first year
56	M	GT	None	251	Normal	No	While matter hyperintensities	No
33	M	GTC	Dilantin	55	Normal	No	Normal	No
21	M	GTC	None	20	Normal	No	T2 hyperintensity R frontal lobe	No but recurrence at 4 years
81	M	Focal to TC	Dilantin	42	Mild intermittent L T slow	No	White matter hyperintensities	No
20	M	GTC	Valproic acid	97	Normal	No	Normal	Yes in 6 months
21	F	GT	Valproic acid	38	Normal	No	Normal	Yes in 1 month
20	M	GTC	None	36	GSW, PSW, 3 Hz SW	No	Normal	Yes, myoclonic jerks in 1 month
17	F	GT	None	45	Normal	No	Normal	No
18	M	GT	None	37	L FTC sharp and spike; gen SW/PS or sharp; R PQ T sharp	Yes — in latter part of EEG epileptiform activity appeared more bilateral/ generalized	Subtle asymmetry hippocampus L>R	Yes in 5 months
37	F	GT	None	41	Normal	No	Normal	No
18	F	GT	None	43	Normal	No	Normal	Yes in 1 month
24	M	GTC	None	32	Normal	No	Normal	No
27	F	GTC	None	227	Normal	No	Normal	No
43	M	Focal	None	64	R T sharp/spike during sleep	Yes — epileptiform discharge seen at 5 hours	Normal	No
32	M	Focal to TC	Dilantin	63	Sharply contoured R FT>L FT	No	Multiple areas of blooming artifact consistent with micro hemorrhage	No
22	M	Focal to TC	None	67	Normal	No	Normal	Yes in 5 months
23	F	GTC	None	39	Normal	No	Normal	No

Table 1. Clinical and EEG features of the patients (*Continued*).

Age	Gender	First seizure type	AED at time of EEG	Time to EEG (days)	EEG findings	Change in EEG after first 30 minutes?	Neuroimaging (MRI unless stated)	Seizure recurrence in first year
48	F	Focal to T	None	71	Intermittent rhythmic delta 3-4 Hz, L>R FT	Yes – longer bursts of slowing and seen on R later in study	4 mm pineal cyst	Yes, in one month. Auras of a flushing sensation
78	M	Focal to TC	Dilantin	71	Normal	No	Pacemaker no MRI. Normal perfusion scan	No
70	M	Focal to TC	Dilantin	174	Normal	No	Pacemaker no MRI	No
57	F	Focal to TC	Dilantin	104	R T sharp/spike; L FT spike	No	CT- resolving R T intraparenchymal hemorrhage and R FP subdural hygroma	No, but remained on an AED (changed to valproic acid)
73	F	Focal to TC	Dilantin	78	Intermittent slowing and sharp and spike waves L T	Yes — epileptiform discharge seen at 1 hour	Normal	No but remained on an AED due to abnormal EEG
20	M	GTC	Lamictal	122	Normal	No	Normal	No
71	F	GTC	Lamictal	148	Intermittent focal slowing L>R CP	No	White matter hyperintensities	No
31	M	GC	None	36	Normal	No	CSF extension in sella	No
20	F	GTC	None	33	Normal	No	Normal	No
59	F	Focal to TC	None	108	Normal	No	White matter hyperintensities	No
39	F	Focal	None	123	Normal	No	Multiple foci of heterotopic grey matter along the margins of the lateral ventricular bodies. Incidental cerebellar tonsillar ectopia	No but started on lamictal due to abnormal MRI
64	F	GTC	None	29	Normal	No	White matter hyperintensities	No
91	M	GT	Lamictal	39	Normal	No	CT- multiple areas of white matter hypoattenuation. Mild generalized atrophy	No but remained on AED due to age

Table 1. Clinical and EEG features of the patients (*Continued*).

Age	Gender	First seizure type	AED at time of EEG	Time to EEG (days)	EEG findings	Change in EEG after first 30 minutes?	Neuroimaging (MRI unless stated)	Seizure recurrence in first year
47	M	Focal to TC	Tegretol	54	L T sharp/spike and sharply contoured theta	Yes — more obvious sharp and spike activity later in the study with deeper sleep	1-cm FLAIR/T2 lesion in R postero-lateral white matter. Stable over time	No but remained on AED
81	F	Focal to TC	Lamictal	54	Normal	No	White matter hyperintensities in keeping with diagnosis of MS	No
56	M	Focal to TC	None	49	L AT spike/sharp seen primarily during sleep	Yes – more obvious epileptiform discharge later in the study	White matter hyperintensities	Yes in 4 months
28	F	Focal to TC	None	145	Sharply contoured slow L>R AT	No	Normal	Yes in 4 months
19	M	GTC	None	126	Normal	No	Normal	No
23	F	Focal to TC	Valproic acid	62	Normal	No	Normal	Yes in 4 months

M: male; F: female; GT: generalized tonic; GTC: generalized tonic clonic; GC: generalized clonic; L: left; R: right; F: frontal; T: temporal; AT: anterior temporal; C: central; P: parietal; PQ: posterior quadrant.

Limitations to recruitment for this study included a lack of space to perform a six-hour EEG, lack of available EEG technologist time, and lack of the ability of some patients to come in for a full day of testing during business hours. It should be noted that these patients were unable to drive and required someone else to bring them in for testing.

Discussion

In keeping with the findings of Burkholder *et al*. (2016), extended EEGs in this population led to an increase of epileptogenic discharge of 5.56%, which in this study correlated to an increased yield of 29%. This later result is impressive since two thirds of the EEGs were entirely normal. Unlike the study of Burkholder *et al*., our study supports the idea that sleep was an important feature for finding epileptiform discharges, as EEG discharge after the first 30 minutes in two patients occurred during sleep. Sleep is more likely during a longer EEG. However, another two patients with epileptiform discharge did not sleep at all during the six-hour study.

Overall, seizure recurrence rates demonstrated a trend towards abnormal EEGs, increasing the risk of seizure recurrence at one year.

Sample size was a limitation of this study. This was due, in part, to resource restrictions as outlined above. Time to EEG was also a limitation in some patients, with at least five patients waiting five to eight months for an extended EEG. Given the rates of recurrence after a first seizure, it might be reasonable to expect that EEGs be performed between one to two months post event. The median range for our center was two months, but certainly this could be improved. It is well known that the closer an EEG is to the time of the event, the more likely it is to be abnormal (Sundaram *et al*., 1990). Given the results, such as those of King *et al*. (1998), timing to EEG may be an equally or even more important aspect for finding epileptiform abnormality on EEG than length of study. The study was also limited by seizure type. As with many first seizure studies (Berg, 2008), most of the patients presented with some form of generalized tonic or tonic-clonic seizure. In 14 patients, it was clear that these events were focal, spreading to bilateral tonic-clonic movements. However, many patients

with first seizure presentations that were focal only were not recruited because they were not referred to the First Seizure Clinic, where most of the recruitment took place.
Finally, EEG demonstrated a better overall utility than MRI in this setting in terms of epilepsy diagnosis.

Conclusion

Extended six-hour EEGs in adult patients with a first seizure increased the yield of epileptiform discharge by 29%. This would translate into nearly a third more patients being diagnosed with epilepsy early on, leading to improved short-term outcomes. EEG is a cheaper test than MRI, even as an extended study. Overall, EEGs were diagnostic of epilepsy in 19% of patients, and MRI in only 3%; CT was diagnostic in one patient. Thus, brain imaging was diagnostic of epilepsy in only 6% of patients overall. Going forward, a larger trial would be needed to further support these findings. □

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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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Dr. Foster has no conflicts of interest to declare.

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TEST YOURSELF

(1) What is the current definition of epilepsy?

(2) What are the risk factors for seizure recurrence in an adult, according to the American Academy of Neurology Guidelines?

(3) What factors increase the yield of epileptiform/epileptogenic discharge on EEG?

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".