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Seizure symptoms and ambulatory EEG findings: incidence of epileptiform discharges

Hai Chen [1], Mohamad Koubeissi [1], Sana Aziz [2], Jeremy D. Slater [3,4], Hashem Al Bunni [5], Muhammad T. Khan [2], Nasser Y. Ali [6], Faraaz A. Khan [7], Amir Alnobani [8], Faraaz M. Hussain [9], Adam U. Syed [10], Anas Fares [11], Talha Iqbal [12], Tanvir U. Syed [13]

[1] Epilepsy Center, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA
[2] Charleston Area Medical Center, Charleston, WV, USA
[3] University of Texas, McGovern Medical School, Department of Neurology, Houston, TX, USA
[4] Chief Medical Officer, The Alliance Family of Companies, Irving, TX, USA
[5] Alfaisal University, College of Medicine, Riyadh, KSA, USA
[6] Medstar Baltimore, Baltimore, MD, USA
[7] Ross University School of Medicine, Portsmouth, Dominica
[8] Midwestern University, Chicago, IL, USA
[9] Case Western Reserve University, Cleveland, OH, USA
[10] Cleveland State University, Cleveland, OH, USA
[11] Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, Cleveland, OH, USA
[12] Talha Iqbal, Ziauddin Medical College, Ziauddin University, Karachi, Pakistan
[13] Neurological Institute, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

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ABSTRACT – *Aims*. Ambulatory video-EEG monitoring has been utilized as a cost-effective alternative to inpatient video-EEG monitoring for non-surgical diagnostic evaluation of symptoms suggestive of epileptic seizures. We aimed to assess incidence of epileptiform discharges in ambulatory video-EEG recordings according to seizure symptom history obtained during clinical evaluation.
Methods. This was a retrospective cohort study. We queried seizure symptoms from 9,221 consecutive ambulatory video-EEG studies in 35 states over one calendar year. We assessed incidence of epileptiform discharges for each symptom, including symptoms that conformed to a category heading, even if not included in the ILAE 2017 symptom list. We report incidences, odds ratios, and corresponding p values using Fisher's exact test and univariate logistic regression. We applied multivariable logistic regression to generate odds ratios for the six symptom categories that are controlled for the presence of other symptoms.
Results. History that included motor symptoms (OR=1.53) or automatisms (OR=1.42) was associated with increased occurrence of epileptiform

Correspondence:
Hai Chen
George Washington University,
School of Medicine and Health Sciences,
2150 Pennsylvania Ave,
NW Washington, DC, 20037, USA
<hachen@mfa.gwu.edu>

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discharges, whereas history of sensory symptoms (OR=0.76) predicted lack of epileptiform discharges. Patient-reported symptoms that were associated with increased occurrence of epileptiform discharges included lip-smacking, moaning, verbal automatism, aggression, eye-blinking, *déjà vu*, muscle pain, urinary incontinence, choking and jerking. On the other hand, auditory hallucination memory deficits, lightheadedness, syncope, giddiness, fibromyalgia and chronic pain predicted absence of epileptiform discharges. The majority of epileptiform discharges consisted only of interictal sharp waves or spikes.
Conclusions. Our study shows that the use of ILAE 2017 symptom categories may help guide ambulatory video-EEG studies.

Key words: EEG, seizure symptoms, ambulatory EEG, epileptiform discharges

Ambulatory video-EEG monitoring (AVEM) is an outpatient procedure and substantially less expensive than inpatient continuous EEG monitoring. AVEM is also less resource-demanding and more accessible to patients, compared to studies in the epilepsy monitoring unit. Commonly, AVEM is used for non-urgent diagnostic evaluation of events, such as differentiation between epileptic and non-epileptic events. Very rarely, AVEM is used for pre-surgical evaluation which may require tapering of medication.

Seizures provoke a variety of potential sensations and behaviors, and an ILAE Task Force summarized common descriptors of those behaviors during a seizure in a recent publication (Fisher *et al.,* 2017). While individual symptoms do not define seizure types, they can be added to the seizure classification to clarify the manifestations of individual seizures (Fisher *et al.,* 2017). In addition, seizure semiology provides crucial information for lateralization and localization of seizures.

Overall, epileptiform activity is reported in 18.0% of AVEM recordings based on a recent study (Syed *et al.,* 2019). EEG focal slowing is a positive predictor of epileptiform abnormalities in AVEM, whereas other features, such as age, MRI findings, and duration of monitoring fail to predict epileptiform discharges (Tolchin *et al.,* 2017). Currently, it is unclear whether semiology description correlates with the incidence of epileptiform discharges. In this study, we utilized a national AVEM cohort to address this question.

Materials and methods

This was a retrospective cohort study. We obtained AVEM outcome and utility data from a single independent diagnostic ambulatory-EEG testing facility (Alliance Family of Companies, Irving, TX) that sets up AVEM in the patient's home. We assessed outcome of AVEM in adult and pediatric cohorts.

Ambulatory video-EEG monitoring

The collaborating ambulatory-EEG testing facility performs AVEM according to a protocol that incorporates, for each patient, 25 electrodes (23 standard 10-20 EEG, two EKG), a 200-sample-per-second EEG recording device worn on the waist with built-in patient-activated pushbutton event monitor and two portable video cameras that are synchronized with EEG recording, and Bluetooth radio hardware for remote real-time monitoring of video and EEG tracings (Lifelines Trackit MK3). For each patient undergoing AVEM, the facility assigns EEG technologists to each carry out one of three roles: AVEM 'setup', 'remote-monitoring', and 'reading'. The 'setup' technologist is responsible for setting up AVEM equipment as well as interviewing patient and caregiver(s) to generate an updated written clinical history relevant to AVEM (*e.g.*, description of events, past medical history, medication list). To maintain quality of AVEM, the 'monitoring' technologist remotely logs in to the AVEM live recording, in real-time, for three minutes every two hours via Bluetooth radio connection in order to identify any technical issue. Once a technical issue is identified and with the patient's permission, the 'setup' technologist is notified and visits the patient at his/her residence to resolve any technical issue. The method has been described in detail in our recent publication (Syed *et al.,* 2019).

Clinical utility variables

Seizure-related symptoms were extracted from patient history and then summarized by an ABPN board-certified neurologist, according to ILAE 2017 descriptors (Fisher *et al.,* 2017). Three neurologists, including two epileptologists, reviewed EEG reports, which included paraphrased clinical history taken from the referring physician, and conformed the historical terminology according to ILAE terms. For those symptoms not found in the ILAE published study, descriptors that were deemed to most precisely reflect patient-reported symptoms were created by the reviewing epileptologist. Abstracted data, such as symptoms as well as other clinical information pertaining to each AVEM that the facility performed between July 1, 2016 and June 30, 2017 was coded into a priori and supplemental variables. Three epileptologists (TUS, MTK, MZK), as a group, reviewed AVEM documentation to determine clinical rationale for each AVEM referral and the outcome. This study only included AVEM recordings that were referred for diagnostic evaluation of events by at least two of these three epileptologists (as opposed to AED adjustment, epileptiform discharge quantification, *etc.*).

Statistical analysis

The incidence of epileptiform discharges in AVTM were reported. We also calculated the percentage of positive findings (epileptifom discharges) in the cohort. Using non-parametric statistical tests (Fisher's exact test and univariate logistic regression), we generated the odds ratio and *p* values that were two-tailed, with probability of Type I error (alpha) of less than 0.05 considered as statistically significant. We also applied multivariable logistic regression to generate odds ratios for the six symptom categories that were controlled for the presence of other symptoms. All statistical analyses were performed using Stata 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

We screened a total of 9,965 recordings, of which 9,221 were analyzed in this study. A breakdown of the 744 excluded recordings is described in our previous publication (Syed *et al.,* 2019). Among those 9,221 recordings, 5,802 were women (62.9%), the median age at the time of study being 53 years (range: 35-67 years). The average duration for monitoring was three days.

Incidence of commonly described symptoms

Seizure-related symptoms were summarized under six categories: automatism, autonomic, cognition, emotion, motor, and sensory, as described previously (Fisher, 2017). In this cohort (*n*=9,221), the most commonly reported symptoms were categorized as sensory (*n*=2447; 26.5%) and cognition (*n*=2189; 23.7%). These were followed by autonomic symptoms (*n*=802; 8.7%), emotional symptoms (*n*=779; 8.4%), automatism (*n*=679; 7.4%), and motor manifestations (*n*=531; 5.8%) (*table 1*). The incidence of individual symptoms varied significantly. For example, under the cognition category (*n*=2,189; 23.7%), 1,992 patients reported memory impairment. However, none of them had reported neglect or forced thinking (*supplementary table 1*). Similarly, anxiety was the most commonly reported symptom among the "emotion" category (48.3%; 376/779), whereas gelastic behavior was not reported (*supplementary table 1*). Nausea was the most commonly reported autonomic symptom (56.6%; 454/802). However, several other symptoms were not reported, such as asystole, erection, hyper/hypoventilation, palpitation, piloerection (*supplementary table 1*). Speech automatism (52.6%; 357/679) was the most commonly described automatism (*supplementary table 1*). Jerking movements (69.3%; 368/531) and headache (71.6%; 1751/2447) were the most commonly described symptoms in the motor and sensory categories, respectively (*supplementary table 1*).

In addition, our study also revealed a number of symptoms that were not included in the current ILAE-published symptom list [1]. These symptoms included lightheadedness (*n*=411; 4.5%), giddiness (*n*=120; 1.3%), syncope (*n*=1,209; 13.1%), urinary incontinence (*n*=159; 1.7%), jerking (*n*=368; 4.0%), fibromyalgia (*n*=412; 4.5%) and headache (*n*=1,751; 19.0%). A complete list of patient-reported symptoms is summarized in *supplementary table 1.*

Table 1. Incidence of common descriptors and epileptiform discharges on EEG.

Common descriptor	Incidence	Epileptiform discharges	Percentage	Odds ratio	*p* value
Cognition	2189	373	17%	0.92 (0.81 – 1.05)	0.204
Emotion	779	137	17.6%	0.96 (0.79 – 1.17)	0.706
Autonomic	802	157	19.6 %	1.13 (0.94 – 1.37)	0.184
Automatism	679	161	23.7%	1.42 (1.18 – 1.72)	<0.001
Motor	531	134	25.2%	1.53 (1.25 – 1.88)	<0.001
Sensory	2447	371	15.2%	0.76 (0.67 – 0.87)	<0.001

Association of EEG findings and specific seizure symptoms

Epileptiform discharges were reported in 18.0% (1,657/9,221) of the recordings. The majority (88.9%) of AVEM with epileptiform discharges showed only interictal discharges, *i.e.* sharp waves or spikes. A detailed description of EEG findings is reported in our previous publication (Syed *et al.*, 2019).

Table 1 summarizes the incidence of epileptiform discharges according to the six major symptom categories. Motor and automatism were independent risk factors for increased occurrence of epileptiform discharges with an odds ratio of 1.53 and 1.42, respectively. On the other hand, the sensory category predicted a lack of epileptiform discharges with an odds ratio of 0.76. For the rest of the categories, cognition and autonomic, the *p* value did not reach statistical significance.

Multiple symptoms were associated with increased occurrence of AVEM epileptiform discharges. These symptoms included lip-smacking (OR=11.56), moaning (OR=5.23), verbal (OR=4.58), *déjà vu* (OR=2.82), muscle pain (OR=2.75), eye-blinking (OR=2.61), aggression (OR=2.48), urinary incontinence (OR=1.82), choking (OR=5.49) and jerking (OR=1.67) (*table 2*). On the other hand, auditory hallucinations (OR=0.16), memory issues (OR=0.88), lightheadedness (OR= 0.73), syncope (OR=0.71), giddiness (OR=0.55), chronic pain (OR=0.29) and fibromyalgia (OR=0.75) predicted the lack of AVEM epileptiform discharges (*table 2*). Statistical significance and odds ratios for symptom categories did not significantly change when controlled for one another in multivariable logistic regression modelling. The complete list of symptoms as well as the corresponding incidence of epileptic discharges, odds ratios and *p* values are described in *supplementary table 1*.

Discussion

We have recently demonstrated a relatively low yield of epileptiform activity in AVEM compared to previously published studies (18% vs 36%) (Faulkner *et al.*, 2012; Syed *et al.*, 2019). This discrepancy is likely due to the difference in sample size and heterogeneity in patient population. Previous data were from a

Table 2. Symptoms and epileptiform discharges.

	Incidence	Epileptiform discharges	Odds ratio	*p* value
COGNITION CATEGORY				
Déjà vu	42 (0.5%)	16 (38.1%)	2.82 (1.51 – 5.28)	0.002
Auditory hallucinations	30 (0.3%)	1 (3.3%)	0.16 (0.02 – 1.15)	0.032
Memory issues	1992 (21.6%)	328 (16.5%)	0.88 (0.77 – 1.00)	0.048
Lightheadedness	411 (4.5%)	57 (13.9%)	0.73 (0.55 – 0.96)	0.025
Syncope	1209 (13.1%)	168 (13.9%)	0.71 (0.59 – 0.84)	<0.001
EMOTION CATEGORY				
Giddiness	120 (1.3%)	13 (10.8%)	0.55 (0.31 – 0.98)	0.041
AUTONOMIC CATEGORY				
Urinary incontinence	159 (1.7%)	45 (28.3%)	1.82 (1.29 – 2.58)	0.001
Choking	11 (0.1%)	6 (54.5%)	5.49 (1.67 – 18.0)	0.007
AUTOMATISM CATEGORY				
Aggression	37 (0.4%)	13 (35.1%)	2.48 (1.26 – 4.89)	0.015
Eye blinking	22 (0.2%)	8 (36.4%)	2.61 (1.09 – 6.24)	0.044
Verbal	14 (0.2%)	7 (50%)	4.58 (1.60 – 13.07)	0.006
Moaning	15 (0.2%)	8 (53.3%)	5.23 (1.90 – 14.45)	0.002
Lip Smacking	35 (0.4%)	25 (71.4%)	11.56 (5.54 – 24.12)	<0.001
MOTOR CATEGORY				
Jerking	368 (4%)	97 (26.4%)	1.67 (1.32 – 2.12)	<0.001
SENSORY CATEGORY				
Chronic pain	50 (0.5%)	3 (6%)	0.29 (0.09 – 0.93)	0.025
Muscle pain	24 (0.3%)	9 (37.5%)	2.75 (1.20 – 6.29)	0.027
Fibromyalgia	412 (4.5%)	59 (14.3%)	0.75 (0.05 – 2.68)	0.049

single-center population and the sample size was relatively small (~300). Our samples were extracted from data from 35 states with the total number of more than 9,000 recordings, and therefore our study may lead to more accurate nation-wide results. The majority of epileptiform discharges were only interictal spikes or sharp waves, and seizures were only found in 125 recordings (1.35% of total recordings). Due to patient safety concerns, seizure provocation procedures, such as medication tapering or sleep deprivation, are not used in the outpatient AVEM. This could explain the low likelihood of capturing a seizure in AVEM procedures.

Symptoms associated with increased occurrence of epileptiform discharges

Our study demonstrated that automatism is associated with increased occurrence of epileptiform discharges with an OR of 1.53. Under this category, lip-smacking, moaning, verbal automatism, blinking or aggression independently predicted increased occurrence of epileptiform discharges.

Automatisms are described as "more or less coordinated adapted involuntary motor activity", often occurring with altered awareness and amnesia (Blume *et al.,* 2001). Oroalimentary automatisms, such as chewing or lip-smacking movements, are the most commonly seen automatisms. Both electrical stimulation and semiological studies suggest that the occurrence of oroalimentary automatisms may result from broad dysfunction of the medial and neocortical temporal structures (Fish *et al.,* 1993; Maillard *et al.,* 2004). The broad involvement of the temporal region may explain the high yield of epileptiform discharges, when oroalimentary automatisms are reported. Vocal automatism is a single or repetitive utterance consisting of sounds such as grunts, whereas verbal automatism consists of words, phrases or brief sentences (Blume *et al.,* 2001). Vocal and speech automatisms are common ictal findings in temporal lobe seizures with an incidence of 50% reported in one study (Gabr *et al.,* 1989). Ictal blinking is smooth blinking of the eyes, not associated with other facial spasms, and secondary to a paroxysmal epileptic discharge. Rhythmical eye blinking, often at a rate of 3 Hz, is frequently observed in focal unaware seizures (Lüders *et al.,* 1998).

Motor movements are further characterized as tonic, clonic, or myoclonic movements in the ILAE 2017 seizure classification (Fisher *et al.,* 2017). Jerking movements were the most commonly reported symptoms in the motor category (69.3%; 368/531). Patients likely have clonic or myoclonic seizures when jerking movements are reported. Therefore, jerking could predict the high likelihood of epileptiform discharges in EEG monitoring.

Other symptoms associated with increased incidence of epileptiform discharges include *déjà vu*, urinary incontinence, choking, aggression and muscle pain. *Déjà vu* is a relatively common psychic aura, regularly seen in temporal epilepsy (Bancaud *et al.,* 1994). Although *déjà vu* can also be seen in the healthy population, the patients in this cohort study mostly likely experienced epileptic *déjà vu*. This is different from physiological *déjà vu* due to a longer duration and increased frequency (Warren-Gash & Zeman, 2014). Urinary incontinence is a relatively common observed symptom and highly specific for convulsive seizures (Oliva *et al.,* 2008). The post-ictal state can present with agitative behavior, explaining aggression as a positive predictor of epileptiform discharges. Post-ictal muscle pain can be attributed to the jerking movements that were previously stated.

Symptoms associated with lack of epileptiform discharges

On the other hand, some symptoms were associated with lack of epileptiform discharges in our study. The sensory category was associated with low likelihood of epileptiform discharges with an OR of 0.76. Among the sensory symptoms, fibromyalgia was a relatively frequently reported symptom (16.8%; 412/2,447) and predicted fewer occurrences of epileptiform discharges (OR=0.75). Also, fibromyalgia was shown to be a predictor for the diagnosis of psychogenic non-epileptic seizures (PNES). PNES are paroxysmal episodes that resemble epileptic seizures, and are psychological (*i.e.,* emotional, stress-related) in origin. Patients with PNES often have more functional somatic syndromes (Dixit *et al.,* 2013; Tatum *et al.,* 2016). We suspect that patients with fibromyalgia were more likely to have PNES instead of epileptic seizure in our cohort, which could explain the low likelihood of epileptiform discharges in the EEG studies.

In this study, many patients were referred due to loss of consciousness/syncope (13.1%, 1,209/9,221) or presyncopal symptoms such as lightheadedness (4.5%, 411/9,221). Syncope could be due to underlying cardiac or neurological disorders, or vasovagal syncope. Our study showed a low yield of AVEM in patients with lightheadedness and syncope. This is consistent with previous routine EEG findings, which showed the incidence of epileptiform discharges in routine EEGs as low as 1.4-1.8% in patients referred due to syncope, similar to those in the healthy adult population (Abubakr and Wambacq, 2005; Dantas *et al.,* 2012). A recent study also suggests that a tilt table EEG test could be more cost-effective than prolonged EEG monitoring (Chen *et al.*, 2019). Our findings further indicate that the etiology of syncope or lightheadedness is likely to be due to other medical conditions instead of epileptic seizures.

The lack of epileptiform discharges may be insufficient to exclude the diagnosis of epilepsy. Scalp EEG is insensitive to tangential-orientated or small, deep electrical dipoles. On average, 8-16% patients with proven epilepsy had no epileptiform discharges during a prolonged video-EEG study (Friedman and Hirsch, 2009; Faulkner *et al.*, 2012; Basiri *et al.*, 2019). Despite the lack of epileptiform discharges, clinical differentiation between a non-epileptic disorder vs "scalp EEG-negative" seizure can often be made based on clinical history, imaging or supportive laboratory data.

Capturing an habitual event is invaluable for the diagnosis. Indeed, AVEM could be effective in providing a diagnosis in two thirds of patients once a habitual event is captured in a previous study (Shihabuddin *et al.*, 1999). Our previous study showed an overall similar rate for capturing an habitual event among patients who underwent AVEM or inpatient video-EEG, and AVTM may be useful to characterize paroxysmal events (Syed *et al.*, 2019).

In summary, patients report various symptoms which could be due to either epileptic seizures or non-epileptic seizure mimics. AVEM is an effective diagnostic tool in event characterization. Some symptoms may be highly specific to epileptic seizures, whereas others may be more likely to be indicative of non-epileptic disorders. Our findings could benefit medical providers in patient consultation and utilization of AVEM.

A limitation of the current study is its retrospective design. Our study included more than 9,000 samples and the conclusions can be further validated in a prospective study with a smaller sample size. We relied on the description of clinical history provided by each referral neurologist to conform the terminology by a group of three neurologists. The inaccuracy of initial clinical history could be an inherent limitation of the study. Due to the study design (no access to clinical notes after the AVEM study), we are unable to identify whether patients without epileptiform discharges had scalp EEG-negative seizures or non-epileptic disorders. Despite the ambulatory findings, we were not aware of the final clinical diagnosis, which often required full evaluation of clinical history, imaging studies and electrophysiological findings. Furthermore, the management changes after AVEM, such as AED initiation/discontinuation, which is important clinical information, remained unclear in our study. □

Supplementary data.

Supplementary table is available on the www.epilepticdisorders.com website.

Disclosures.

Dr. Jeremy Slater is the chief medical officer of Alliance Neurodiagnostics.

The other authors have no conflict of interest to declare.

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