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Focal seizures without awareness

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Abstract
Objective: To characterize patients with seizures that only occur without their awareness (SWA).
Methods: Twenty-four patients with SWA were retrospectively identified by chart review and subsequently underwent video-EEG monitoring (VEM). Eleven patients met selection criteria for SWA and were never aware of any seizures. A case-matched control group of patients who were always aware (SA) was used for comparison. Statistical analysis included Pearson's Chi-square, Fisher's Exact, and Mann—Whitney.
Results: Patients with SWA were older at seizure diagnosis than those with SA ($p = 0.04$), were less often referred for evaluation of seizures or epilepsy ($p = 0.04$), and were referred faster for VEM, despite SWA were significantly less likely to include motor manifestations ($p = 0.0004$). SWA more often had temporal lobe onsets ($p < 0.0001$) with left lateralization on ictal EEG ($p < 0.0001$). At final follow up, patients with SWA had tried fewer antiseizure drugs ($p = 0.03$), but reported seizure freedom as often as patients with SA ($p = 0.4$).
Significance: We suggest that patients with SWA have a unique epilepsy syndrome. Patients with absent recall were older, referred later, had fewer motor signs, and dominant hemisphere limbic localization than patients with SA, but fewer antiseizure drugs are used in treatment. Patients with SWA can be detected from the clinical history, though serial VEM is needed to validate effective management.

Introduction

Accurate seizure self-reporting is the principal means to identify and quantify seizure frequency both for routine patient management and approval of antiseizure drugs (ASD) by the U.S. Food and Drug Administration. However, a significant number of patients with epilepsy exhibit only partial recall for their seizures after they have occurred (Heo et al., 2006; Blum et al., 1996; Tatum et al., 2001; DuBois et al.,

Abbreviations: ASD, antiseizure drugs; IED, interictal epileptiform discharges; QoL, quality of life; SA, seizure awareness; SWA, seizures without awareness; VEM, video-EEG monitoring.

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2010). Poor patient recall of the ictus is a form of anosognosia, but it implies a retrieval processing deficit. Prior reports suggest that when it is coupled with a subtle clinical semiology, limited patient observation or nocturnal predisposition seizures may be unrecognized or go unnoticed for years (Zangaladze et al., 2008; Heo et al., 2006; Tatum et al., 1998). Additionally, seizures without awareness (SWA) may involve encoding memories or retrieval deficits coupled with a prolonged post-ictal state and mimic other physiological conditions, such as Alzheimer's disease or Transient Global Amnesia (Tatum et al., 1998; Mosbah et al., 2014). This can result in both a *missed treatment* of the correct condition (epilepsy) and the *mistreatment* of an incorrect neurological or psychiatric condition. Previously, it was shown that 30% of patients undergoing video-monitoring were never aware of any seizures and only 26% identified all seizures (Blum et al., 1996). Even in the home environment, 11/47 seizures (23.4%) during ambulatory EEG were solely detected by the computer reflecting patient and observer unawareness (Tatum et al., 1998). Because identification and quantification of seizures and epilepsy syndromes is crucial to expedite an appropriate treatment, we sought to characterize a subset of epilepsy patients who only experience SWA by comparing a similar cohort of age and gender matched patients with focal epilepsy who always demonstrated seizure awareness (SA).

Material and methods

The medical records of 692 patients from a single tertiary care outpatient epilepsy clinic were reviewed between June 2009 and April 2013 for patients suspected to manifest only SWA based upon observer report of seizures occurring without recognition by the individual. The study was approved by the Mayo Clinic institutional review board for the safety of human subjects. SWA were defined as seizures that occurred spontaneously without patient recognition at any time before, during, or following the seizure. Our inclusion criteria allowed only adults with focal seizures. We also required video-EEG monitoring (VEM) confirmation of SWA and SA in every case. Patients with non-epileptic seizures and seizures with any component of awareness were excluded. Patients with generalized epilepsy, abnormal cognition, a lesional MRI, and patients under 18 years of age were excluded to homogenize patients into a pure cohort. Patients without VEM were also excluded to ensure confirmation of SWA by failing to activate the nurse call button or the push button alarm. In the outpatient setting, a patient with SWA was required to have verification by an observer that a complete absence of awareness for every seizure witnessed occurred. In addition the patient needed to deny awareness and a few patients denied or confabulated why witnesses reported a history of ''spells''. During VEM we required the presence or absence of push-button activation and verbal absence or presence of SA upon nursing cue after a seizure occurred.

The medical records and VEM results of an age (±5 years) and gender case-matched control SA group was composed of a cohort of patients who were always aware of their seizures by personal and witness accounts. The same exclusion criteria were applied to the SA group with the notable exception that they were always able to call for help prior to their seizures during VEM. Patient demographics included age, sex, duration following the first reported event, frequency of events, and risk factors for epilepsy. Furthermore, we analyzed the number of VEM recorded seizures, ictal semiology, seizure localization, and lateralization. Subclinical seizures were assessed in addition. Because subclinical seizures by definition lack clinical signs and is potentially confused with SWA, we restricted the use of this term to a focal seizure with a duration (<10 s), restricted field of electrographic distribution (hemispheric or lobar maximal propagation) and an expected lack of associated clinical effect. Seizure freedom (seizure calenders), number of ASD trialed, and epilepsy surgery status were assessed at the follow-up visit after VEM (range 3—12 months). Statistical differences between patient groups were measured by Pearson's Chi-Square where sample size allowed, Fischer's Exact Test, and Mann—Whitney *U* test where non-parametric data was analyzed.

Results

Demographics

A total of 692 outpatients were evaluated between 6/2009 and 4/2013. Twenty-four patients were assessed for study eligibility. Of 24 non-lesional epilepsy patients suspected of only having SWA and a normal brain MRI, 13 did not meet inclusion criteria (nine were not validated by VEM, two were found to exhibit partial awareness of some seizures, and two patients did not have any seizures during VEM). The remaining 11 patients comprised a homogeneous cohort of patients with complete unawareness of seizures suspected clinically and then confirmed by VEM. The SWA group had a mean age of 58 years (SD 21.6), and 4/11 (36%) were female. Some patients had a prior empiric trial of ASDs without diagnosis, though about half were not taking any at the time of initial evaluation. A similar control group of patients who were always aware of seizures was identified from their admission for VEM and validated by the clinical history. The mean age of the case-matched SA cohort was 53 years (SD 22.3), and 4/11 (36%) were female.

Awareness

Patients with SWA were older (53 vs 33 years) at the first witnessed event ($p = 0.04$) (Figure 1A). When classified as either medical (SWA = 1, SA = 1), traumatic (SWA = 2, SA = 3), or no risk factors (SWA = 8, SA = 7), differences between groups were minimal ($p = 1.0$). The onset of symptoms prior to presentation at our center was 4.8 years (SD 3.16) for SWA and 19.8 years (SD 15.3) for SA.

Five of 11 SWA patients (45%) were referred for evaluation of ''possible seizures'', five for ''spells'', and one for episodic dizziness. Eight of 11 (91%) SA patients were referred for treatment of uncontrolled seizures, two (18%) for possible seizures, and one for spells ($p = 0.04$). All 11 SA patients provided estimates of their seizure frequency, while only nine of 11 (82%) SWA patients provided witness estimates prior to VEM. When classified into daily, weekly, monthly, and yearly seizure frequencies, available estimates