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Brief Communication

Antiepileptic drug reduction and increased risk of stimulation-evoked focal to bilateral tonic–clonic seizure during cortical stimulation in patients with focal epilepsy

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A B S T R A C T

Introduction: Stimulation-evoked focal to bilateral tonic–clonic seizure (FBTCS) can be a stressful and possibly harmful adverse event for patients during cortical stimulation (CS). We evaluated if drug load reduction of antiepileptic drugs (AEDs) during CS increases the risk of stimulation-evoked FBTCS.

Material and methods: In this retrospective cohort study, we searched our local database for patients with drug-resistant epilepsy who underwent invasive video-EEG monitoring and CS in the University Hospital la Fe Valencia from January 2006 to November 2016. The AED drug load was calculated with the defined daily dose. We applied a uni- and multivariate logistic regression model to estimate the risk of stimulation-evoked FBTCS and evaluate possible influencing factors. Furthermore, we compared patients whose AEDs were completely withdrawn with those whose AEDs were not.

Results: Fifty-eight patients met the inclusion criteria and were included in the analysis. Stimulating 3806 electrode contact pairs, 152 seizures were evoked in 28 patients (48.3%). Ten seizures (6.6%) in seven patients (12.1%) evolved to FBTCS. In the univariate and multivariate analysis, a 10% reduction in drug load was associated with an increase of the odds ratio (OR) of stimulation-evoked FBTCS by 1.9 (95%-CI 1.2, 4.0, p-value = 0.04) and 1.9 (95%-CI 1.2, 4.6, p-value = 0.04), respectively. In patients, whose AEDs were completely withdrawn the OR of FBTCS increased by 9.1 (95%CI 1.7, 69.9, p-value = 0.01) compared with patients whose AEDs were not completely withdrawn. No other factor (implantation type, maximum stimulus intensity, number of stimulated contacts, history of FBTCS, age, gender, or epilepsy type) appears to have a significant effect on the risk of stimulation-evoked FBTCS.

Conclusions: The overall risk of stimulation-evoked FBTCS during CS is relatively low. However, a stronger reduction and, especially, a complete withdrawal of AEDs are associated with an increased risk of stimulation-evoked FBTCS.

1. Introduction

Many epilepsy centers around the world use cortical stimulation (CS) to explore eloquent cortex or define the epileptogenic zone during invasive video-EEG monitoring [1,2]. However, this procedure can be time consuming and unpleasant for patients. An important adverse event during CS is the occurrence of stimulation-evoked secondary generalized tonic–clonic seizure, or focal to bilateral tonic–clonic seizure (FBTCS) according to the new seizure classification proposal of the International League Against Epilepsy (ILAE) [3,4]. While, according to some experts, typical focal seizure (FS) evoked by CS may help define the epileptogenic zone, a stimulation-evoked FBTCS is usually an unwanted by-product and is probably a health risk for the patient [1,3]. For example, FBTCS during video-EEG monitoring can lead to injuries such as vertebral compression fractures [5]. In addition, higher frequencies of FBTCS during video-EEG monitoring may cause postictal psychosis [6]. In the worst case scenario, FBTCS may even cause sudden

Abbreviations: AEDs, antiepileptic drugs; FBTCS, focal to bilateral tonic–clonic seizure; CI, confidence interval; CS, cortical stimulation; DDD, defined daily dose; FS, focal seizure; ILAE, International League Against Epilepsy; OR, odds ratio; PI, posterior interval; SE, status epilepticus; SUDEP, sudden unexpected death in epilepsy.

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unexpected death in epilepsy (SUDEP) [7]. Thus, reducing the risk of FBTCS may make CS less stressful and safer for patients. In the last two decades, the safety of patients during video-EEG monitoring has become more important and now constitutes a prime focus of clinical investigation [5,8]. While some studies have already identified risk factors for spontaneous FBTCS during prolonged video-EEG, such as withdrawal of antiepileptic drugs (AEDs) or a previous history of FBTCS, little is known about the risk factors of FBTCS evoked by CS [9–11]. In this study, we investigate potential risk factors of stimulation-induced FBTCS. We hypothesized that a reduction of AEDs during video-EEG monitoring and CS is associated with a higher risk of stimulation-evoked FBTCS.

2. Material and methods

2.1. Patients

Our local database was screened for patients with drug-resistant epilepsy who underwent video-EEG in the multidisciplinary epilepsy unit of the University Hospital *La Fe* in Valencia from January 2006 to November 2016. The following inclusion criteria for the final analysis were used: patients must have undergone (1) invasive video-EEG monitoring and (2) CS to be included. Data were taken from the patient clinical records. The study was approved by the local medical ethical committee of the University Hospital *La Fe*, Valencia.

2.2. Data collection

2.2.1. Implantation and invasive video-EEG monitoring

Invasive video-EEG monitoring was performed on patients where noninvasive presurgical workup (cerebral magnet resonance imaging [MRI], scalp video-EEG monitoring, neuropsychological tests, intracarotid amobarbital testing, fluorodeoxyglucose-positron emission tomography, subtraction ictal single-photon emission computed tomography, and coregistered with MRI) had been inconclusive to further delimitate the epileptogenic zone and explore eloquent cortex. Two distinct implantation techniques were used: 1. subdural electrodes (strip and grid cortical electrodes, Cortac®, PMT Corporation, Chanhassen, USA); or 2. depth electrodes (Depthalon®, PMT Corporation, Chanhassen, USA). The implantation schemes were performed on each patient based on semiology and the result of the noninvasive presurgical workup. The correct electrode placement was verified by coregistering cerebral MRI before implantation and cerebral computer tomography after implantation. Patients were transferred to the epilepsy-monitoring unit the day after implantation.

2.2.2. Drug load reduction

Antiepileptic drugs were reduced according to clinical criteria to facilitate seizure recording from the day after implantation. The total drug load was quantified with the defined daily dose (DDD) according to the Collaborating Centre for Drug Statistics methodology of the World Health Organization. The DDD reflects the 'assumed average maintenance dose per day' for drugs used in different medical fields, in this case, preventing patients from having epileptic seizures (http://www.whocc.no/atc_ddd_index/). For each patient, the daily dose of a specific AED at baseline (before AED reduction) and the minimal daily dose during CS were related to the respective DDD by calculating the respective ratio (daily dose/DDD). The total DDD was calculated by summing the DDD of all AEDs of the individual regimen for baseline and during CS. The total drug load reduction was calculated by one minus the ratio of the total DDD during CS and total DDD at baseline for each patient (total DDD CS/total DDD baseline), so that 0% represents no reduction and 100% represents complete withdrawal of AEDs. Because a 1% reduction is not very likely to have a meaningful effect, we scaled the variable using a 10% scale.

2.2.3. Cortical stimulation

Cortical stimulation was applied with the Osiris Neurostimulator device (Inomed Medizintechnik GmbH, Emmendingen, Germany) towards the end of the invasive presurgical workup, usually after having recorded spontaneous seizures. In all patients, each electrode contact was stimulated using an adjacent electrode contact (1 vs. 2, 2 vs. 3, etc.) with a bipolar impulse of a 5-second duration with a frequency of 50 Hz and a pulse width of 300 ms with an intensity from 1 to 15 mA or from 1 to 10 mA starting at 1 mA and rising in the following steps: 3 mA, 5 mA, 7 mA, 10 mA, 13 mA, and 15 mA; as long as patients were able to tolerate it; or until a clinical response or seizures were observed. Electrodes were retested, in the case of a positive clinical or electrical response. Stimulation-evoked seizures were defined as series of afterdischarges that evolved, spread, and were associated with clinical symptoms [3]. Seizures were categorized according to the operational classification proposal for seizure types made by the ILAE in focal seizure not evolving to bilateral tonic–clonic seizure (FS, correspond to simple and complex partial seizure without secondary generalization in the classification from ILAE 1981), or focal to bilateral tonic–clonic seizure (FBTCS corresponds to seizure with partial onset and secondary generalization in the ILAE classification from 1981) [4,12].

2.3. Statistical analysis

We applied a logistic regression model to evaluate possible influencing factors on the risk of stimulation-evoked FBTCS. As the dependent variable, we entered occurrence of FBTCS as the binary outcome (*yes* indicating presence, and *no* indicating absence of FBTCS) into the model. As independent variables, we entered: the history of spontaneous FBTCS (positive or negative); drug load reduction (% reduction of DDD on a 10% scale during CS compared with baseline); sex (female or male); type of epilepsy (temporal lobe epilepsy or extra-temporal lobe epilepsy); age; maximum stimulus intensity per patient (10 mA or 15 mA); number of implanted electrode contacts per patient; hemisphere of implantation (left, right, or bilateral); and type of implanted electrodes (subdural or depth electrodes). If drug load reduction increased the risk of stimulation-evoked FBTC, then risk should be the highest in patients without AEDs (corresponding to a 100% drug-load reduction). Therefore, we compared the occurrence of FBTCS in patients where AEDs were completely withdrawn with occurrence in patients where AEDs were not completely withdrawn. For this purpose, we replaced the variable drug load reduction with a binary variable in the model (1 indicating 100% drug-load reduction and 0 indicating a drug-load reduction of less than 100%). Propensity score analyses were used to adjust for potential confounders [13]. P-values of less than 0.05 were considered significant. We used univariate and multivariate analyses. Since logistic regression can be biased in rare events such in the case of our dependent variable stimulation-evoked FBTCS, we performed a sensitivity analysis with a multivariate Bayesian logistic regression model using a weakly informative prior with a Cauchy distribution [14]. Bayesian 95% posterior intervals (PI), which resemble frequentist 95% confidence intervals (CI), were drawn from the posterior distribution using the *Markov chain Monte Carlo* method with 10,000 iterations [15]. Graphical presentation and statistical analysis were performed with R version 3.4.0 (R Foundation of Statistical Computation, Vienna, Austria) and the packages ggplot 2 version 2.2.1, rstanarm version 2.15.2, and dplyr version 0.5.0.

3. Results

3.1. Clinical characteristics

Between January 2006 and November 2016, 847 patients were monitored with video-EEG telemetry. Of those, 58 patients with drug-resistant epilepsy were implanted with intracranial electrodes and further explored with invasive video-EEG telemetry including CS (Table 1).