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After-discharges and seizures during pediatric extra-operative electrical cortical stimulation functional brain mapping: Incidence, thresholds, and determinants

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HIGHLIGHTS

- Electrical cortical stimulation shows high incidence of after-discharges (77%) and seizures (35%)
- Current thresholds for after-discharges show a significant linear decreasing trend with age.
- After-discharges predict 3.5 times higher odds of having a seizure during cortical stimulation.

ABSTRACT

Objective: This study examined the incidence, thresholds, and determinants of electrical cortical stimulation (ECS)-induced after-discharges (ADs) and seizures.
Methods: Electrocorticograph recordings were reviewed to determine incidence of ECS-induced ADs and seizures. Multivariable analyses for predictors of AD/seizure occurrence and their thresholds were performed.
Results: In 122 patients, the incidence of ADs and seizures was 77% (94/122) and 35% (43/122) respectively. Males (odds ratio [OR] 2.92, 95% CI 1.21–7.38, $p = 0.02$) and MRI-negative patients (OR 3.69, 95% CI 1.24–13.7, $p = 0.03$) were found to have higher odds of ECS-induced ADs. A significant trend for decreasing AD thresholds with age was seen (regression co-efficient −0.151, 95% CI −0.267 to −0.035, $p = 0.011$). ECS-induced seizures were more likely in patients with lateralized functional imaging (OR 6.62, 95% CI 1.36–55.56, $p = 0.036$, for positron emission tomography) and presence of ADs (OR 3.50, 95% CI 1.12–13.36, $p = 0.043$).
Conclusions: ECS is associated with a high incidence of ADs and seizures. With age, current thresholds decrease and the probability for AD/seizure occurrence increases.
Significance: ADs and seizures during ECS brain mapping are potentially hazardous and affect its functional validity. Thus, safer method(s) for brain mapping with improved neurophysiologic validity are desirable.

1. Introduction

Electrical cortical stimulation (ECS) is the standard method for pre-surgical mapping of cortical function, particularly language and motor cortices, to optimize safety and efficacy of epilepsy surgery. However, ECS is known to be associated with the risks of after-discharges (ADs) and seizures, with several neurophysiological implications (Jayakar and Lesser, 2008). ADs can potentially

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evolve into electrographic or electro-clinical seizures, even when the stimulated brain region is not known to generate spontaneous seizures (Blume et al., 2004). ADs can also compromise the interpretation of the results of ECS, since it is difficult to ascertain if an observed functional response was due to stimulation current or ADs. Sometimes, ADs can propagate to electrodes away from the site of stimulation, which raises concerns about functional localization to the vicinity of stimulated cortex versus areas with preferential remote connectivity (Lesser et al., 1987). Several aspects of ECS-induced ADs and seizures remain poorly understood in children. Current thresholds for eliciting ADs have shown a high degree of within-subject and inter-individual variability (Lesser et al., 2008; Pouratian et al., 2004). Essentially, the predictors for occurrence and current thresholds for ECS-induced ADs and seizures remain undefined. We performed a retrospective review for occurrence of extra-operative ECS-induced ADs and seizures, in children with subdural electrodes, to elucidate the factors associated with occurrence of ADs, ECS-induced seizures, and determinants of their current thresholds.

2. Methods

2.1. Patient sample

The epilepsy surgery database at Cincinnati Children's Hospital was reviewed to identify patients who underwent pre-surgical monitoring with intracranial electrodes between January 2007 and December 2014. Patients who underwent ECS functional mapping were included. ECS functional mapping was performed in patients with concern for potential overlap between cortical areas sub-serving motor and/or language function and the proposed resection. Patients who were unable to cooperate and complete the procedure were excluded. The study was approved by the institutional review board (IRB 2015-6342).

2.2. Extra-operative Electrocorticography (ECoG) recordings

We used subdural electrodes consisting of 4.75 mm platinum/iridium discs embedded in silicone elastomer having 2.5 mm exposed contacts and a center-to-center distance of 1 cm (Auragen, Integra Neurosciences, Plainsboro, NJ). A distant 2-contact subdural strip facing the dura served as the reference and ground. The configuration and location of the grids and strips were at the discretion of the attending epileptologist. Electrode position relative to the underlying cortex was determined by direct observation in the operating room and confirmed by co-registration of pre-implantation volumetric brain magnetic resonance imaging (MRI) with post-implantation head computed tomographic scan. Extra-operative ECoG was recorded using Bio-Logic Ceegraph XL-II amplifiers (Bio-Logic Systems Inc., Mundelein, IL, USA) at 0.1–400 Hz before April 2008, in 17 patients, and subsequently using Stellate eAmp (Stellate Systems Inc., Montreal, Quebec, Canada) at 0.1–667 Hz in all other patients.

2.3. Electrical cortical stimulation

Extra-operative bipolar ECS was performed using OCS2 Ojemann cortical stimulator (Integra Life Sciences, Plainsboro, NJ). Electrode pairs were sequentially stimulated with biphasic square-wave pulses at the following initial settings: pulse frequency 50 Hz, pulse duration 0.3 ms, train duration 2 s for motor mapping and 5 s for language mapping, and stimulus intensity 2 mA. Stimulus current was increased by 1–2 mA until: (a) a functional response occurred, (b) prolonged ADs/seizure was triggered, (c) maximum current of 10 mA was attained. In case of ADs, sometimes the stimulus intensity was reduced by 25%, pulse duration was increased to 0.5–1 ms and repeat stimulation was attempted. This was done to ensure delivery of the similar energy density at that electrode pair, while trying to avoid an iatrogenic seizure (Jayakar et al., 1992). Simultaneous ECoG was recorded throughout the ECS session. For latter (n = 26) patients, ECS was performed using Natus Cortical Stimulator (Natus Medical Inc., Middleton, WI). The procedure was identical, except that the maximal current strength for the instrument was 15 mA.

2.4. Data extraction

Following data was extracted for each patient: (a) demographic data: gender, handedness; (b) pre-surgical evaluation: age of onset of seizures, anti-epileptic drugs (AEDs), seizure frequency, full scale intelligence quotient (FSIQ), lateralization of seizure semiology, interictal and ictal scalp EEG, interictal FDG positron emission tomography (PET), subtraction ictal single photon emission computed tomography (SPECT) co-registered to MRI (SISCOM), magnetoencephalography (MEG), presence and location of brain MRI lesion, and language lateralization by verb generation paradigm on functional MRI; (c) surgical information about brain lobe(s) and sublobar areas covered by subdural electrodes, and localization of ictal onset; (d) ECS information: age at the ECS, brain lobe (s) stimulated, occurrence of ADs and ECS-induced seizures, current thresholds for ADs and seizures; (e) histology of the resected brain tissue. Extra-operative ECoG data during ECS were again reviewed for the study purposes for all subjects, blinded to the clinical report. PET/SISCOM were classified as being clearly lateralized (unilateral abnormalities either on right or left side) or not (normal or bilateral abnormalities). All pre-surgical modalities were also classified as concordant or discordant depending on correspondence to the side of ECS.

2.5. Outcome measures and definitions

Outcomes include proportion of patients with ADs and ECS-induced seizures, current thresholds for occurrence of ADs and ECS-induced seizures, and if a rescue medication was used for ECS-induced seizure. ADs were defined as rhythmic discharges (spikes, poly-spikes, sharp waves or spike-wave complexes) which were clearly distinct from pre-stimulation electrographic activity and occurred immediately following ECS (Blume et al., 2004; Chatrian et al., 1974). AD threshold was defined as the lowest current (mA) of stimulation that resulted in the occurrence of AD train lasting >3 s. ECS-induced seizures were defined as trains of ADs that evolved in terms of distribution, morphology, and/or frequency, and were accompanied by clinical manifestations. Seizure threshold was defined as the minimum stimulation current (mA) that resulted in an ECS-induced seizure. The highest current which failed to elicit the response, was not used to define AD/seizure threshold (Blume et al., 2004). Whether the clinical manifestations were sufficient for characterization of an evolving run of ADs as a seizure, and the decision to use rescue medication, were at the discretion of the physician performing the ECS.

2.6. Statistical analysis

Data were extracted on to a spreadsheet and examined for inconsistencies. Demographic variables, pre-surgical modalities, age at the time of ECS, and post-operative histology were compared between groups of patients with/without ADs, with/without ECS-induced seizure(s), and those who received/did not receive rescue medication for an ECS-induced seizure. These univariate comparisons for frequencies (categorical variables) and means (continuous variables) were performed with Fisher exact test and