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Intracranially recorded ictal direct current shifts may precede high frequency oscillations in human epilepsy

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HIGHLIGHTS

- Either ictal direct current shifts or high frequency oscillations were observed in more restricted areas than conventional ictal changes.
- Both ictal direct current shifts and high-frequency oscillations contributed to delineate the core of tissue generating epileptic seizures.
- The earlier occurrence of ictal direct current shifts than high frequency oscillations may suggest an active role of glia in seizure generation.

ABSTRACT

Objective: We assessed the temporal–spatial characteristics of ictal direct current (DC) shifts (or infraslow activity) and high frequency oscillations (HFOs) in 16 patients with intractable focal epilepsy.
Methods: The underlying etiology consisted of cortical dysplasia, glioma, hippocampal sclerosis, and low-grade neuroepithelial tumor in nine, four, two, and one patients, respectively. The median number of analyzed seizure events was 8.0 per patient (range: 2–10). Chronic electrocorticographic recording was performed with (1) a band-pass filter of 0.016–600 Hz (or 0.016–300 Hz) and a sampling rate of 2000 Hz (or 1000 Hz).
Results: Ictal DC shifts and a sustained form of ictal HFOs were observed in 75.0% and 50.0% of the patients, and 71.3% and 46.3% of the analyzed seizures. Visual assessment revealed that the onset of ictal DC shifts preceded that of ictal HFOs with statistical significance in 5/7 patients. The spatial extent of ictal DC shifts or HFOs was smaller than that of the conventionally defined seizure onset zone in 9/12 patients.
Conclusion: Both ictal DC shifts and HFOs might represent the core of tissue generating seizures.
Significance: The early occurrence of ictal DC shifts warrants further studies to determine the role of glia (possibly mediating ictal DC shifts) in seizure generation.

1. Introduction

Digital electroencephalographic (EEG) technology has enabled us to clinically record and analyze wide-band EEG in epilepsy patients undergoing surgery in the 21st century (Ikeda et al.,

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1996; Bragin et al., 2005; Worrell et al., 2008; Jacobs et al., 2009). EEG components <1 Hz and >200 Hz can be reliably recorded. While spikes and sharp waves are considered as epileptogenic markers in conventional EEG, ictal direct current (DC) shifts, or infraslow activity, and high-frequency oscillations (HFOs) are also implicated as epileptogenic markers in wide-band EEG. The terminology of slow activity will be discussed later.

Ictal DC shifts or slow shifts were initially investigated in animals in 1960s (Gumnit and Takahashi, 1965; Gumnit et al., 1970), and were suggested to reflect the activity of glias and pyramidal neurons (Speckmann and Elger, 1999). Technical difficulty to eliminate artifacts and lack of appropriate electrode material and input impedance of EEG amplifier, however, limited the recording of ictal DC shifts in humans. Ictal DC shifts were therefore largely abandoned for the following 30 years in human epilepsy research. Intracranial seizure onset had been defined with conventional frequency activity (beta, alpha, theta, and delta activities), repetitive spikes, attenuation, and high gamma activities (40–80 Hz) until the 1980s.

Ictal DC shifts, however, were reappraised in human epilepsy in the 1990s (Ikeda et al., 1996, 1999; Gross et al., 1999; Hughes et al., 2005; Mader et al., 2005; Thordstein et al., 2005; Rodin et al., 2006, 2008, 2009; Ikeda, 2008; Rodin and Modur, 2008; Ren et al., 2011; Constantino and Rodin, 2012; Rampp and Stefan, 2012; Shih et al., 2012). Ictal DC shifts were first successfully recorded in human intractable neocortical epilepsy with subdural electrodes using alternate current (AC) amplifier with large input impedance of 200 MΩ and with time constant (TC) 10 s, instead of DC amplifier (Ikeda et al., 1996, 1999; Ikeda, 2008), and were reported as an epileptogenic marker for the first time in humans.

Ictal DC shifts were originally defined as slow potential not detected by a low-frequency filter (LFF) of 1.0 Hz, but detected by opening LFF to 0.016 Hz, and the upward or downward phase of each slow shift lasted at least 3 s (Ikeda et al., 1999). In the analysis of subdural recording in 24 patients with medically refractory partial epilepsy, 23 of 24 patients (96%) showed ictal DC shifts (Ikeda, 2008). The occurrence rate was 87 (42–100)% of seizures in each patient. Ictal DC shifts were mainly negative in polarity (21/23 patients) and were recorded regardless of etiology or epilepsy type. Ictal DC shifts occasionally occurred later than conventional ictal EEG pattern or clinical onset, which presumably reflected the recruiting process in the middle of seizures. Similar findings followed, and even interictal infraslow activity is paid attention (Ren et al., 2011; Rodin et al., 2014).

HFOs were initially investigated by unit recording in animals before digital EEG technology facilitated the recording of fast activity above 50 Hz. They are clinically well recognized by intracranial electrodes as field potentials and are studied extensively in the field of epilepsy surgery (Ochi et al., 2007; Jacobs et al., 2008). Pathological HFOs in epilepsy primarily reflect clusters of action potentials of pyramidal cells and interneurons.

HFOs are usually defined as oscillatory activities higher than 80 Hz. Generally, 80–200 Hz activities are called ripples, and 250–500 Hz fast ripples. The inhibitory mechanism by interneurons is maintained in ripples (Jefferys et al., 2012), while fast ripples reflect hypersynchronous population spikes of excitatory pyramidal cells. Fast ripples are regarded as more related to ictal epileptogenicity in animals and humans (Bragin et al., 1999a,b, 2005). Fast ripples are suggested to reflect seizure onset zone more specifically in animals (Bragin et al., 1999b) and have been extensively investigated in humans (Jacobs et al., 2009).

Modur et al. analyzed ictal HFOs (>70 Hz) in six patients with neocortical epilepsy (Modur et al., 2011). Smaller resections, restricted mainly in the cortices generating HFOs with evolution, were correlated to favorable seizure outcome.

The novel biomarkers of human epileptogenicity are now to be delineated and require further investigations. Based on the previous studies, both ictal DC shifts and HFOs seem to be useful biomarkers independently or together to detect the epileptogenic zone. Their application for the diagnosis and management of epilepsy is expected, namely for epilepsy surgery and seizure prediction. The relationship among ictal DC shifts, HFOs, and conventional ictal EEG change, however, is yet to be elucidated. A few manuscripts including ours (Modur and Scherg, 2009; Imamura et al., 2011; Modur et al., 2012; Wu et al., 2014) or only an abstract (Erbayat Altay et al., 2011) have shown the relation between ictal DC shifts and HFOs. We previously revealed that both ictal DC shifts and HFOs were located in the same area and were useful to detect the ictal onset zone (Imamura et al., 2011). As far as we know, it was also the first report which clearly showed ictal DC shifts preceded HFOs. The systematic analysis of phase–amplitude coupling of ictal HFOs and infraslow activity was previously performed, where it was not concluded that the onset of ictal infraslow activity preceded that of HFOs (Nariai et al., 2011a).

To assess the clinical usefulness of ictal DC shifts and HFOs for delineating the epileptogenic zone, we analyzed and compared the two with the conventional ictal pattern recorded intracranially in 16 patients with intractable partial epilepsy in terms of (1) occurrence rate, (2) relative onset time among the three activities, and (3) correlation with pathology.

With regard to the terminology, DC shifts could be recorded not only with DC amplifier but also well with AC amplifier with long TC such as 10 s (Ikeda et al., 1996). It might be more precise to call them "DC shifts" when recorded with a DC amplifier. When recorded with an AC amplifier with long TC, they could be simply called "slow shifts", "very slow", "baseline shifts", or "infraslow activity" (Rodin and Modur, 2008; Kim et al., 2009). In this manuscript, however, we shall use the term of ictal "DC shifts" because potentials even recorded with an AC amplifier with a long TC of 10 s could contain the feature of DC shifts, and because it has been used interchangeably in the previous literatures.

2. Methods

2.1. Patients (Fig. 1 and Table 1)

We conducted an observational study on 16 patients (six females and 10 males). They had intractable partial epilepsy and had chronic intracranial electrode implantation for presurgical evaluation to define seizure onset zone and eloquent areas from June 2008 to July 2012. Two patients with chronic intracranial electrode implantation during the period were excluded because one patient had no spontaneous seizures and the other patient only had one subclinical seizure. Age at seizure onset was 13.2 ± 10.5 (mean ± standard deviation) years, and age at epilepsy surgery 28.9 ± 7.6 years. The pathological diagnosis was as follows: focal cortical dysplasia (FCD) only = 9, glioma with or without FCD = 4, hippocampal sclerosis (HS) = 2, and low-grade neuroepithelial tumor = 1. Patient 4 in the present manuscript was previously reported as a case report (Imamura et al., 2011). In Patients 1 and 2 (glioma without FCD), magnetic resonance imaging (MRI) showed active and partly destructive feature in the glioma lesion such as necrosis and surrounding edema. Patients 3 and 4 (glioma with FCD) had a long history of intractable epilepsy over 8–33 years. 18F-fluorodeoxyglucose-positron emission tomography was done in 15 patients. Three patients had ictal single-photon emission computed tomography imaging. Concordance of lateralization or localization of seizure focus in those noninvasive examinations was taken into account before epilepsy surgery in case conference.