Clinical Neurophysiology 129 (2018) 59–68

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Frontal infraslow activity marks the motor spasms of anti-LGI1 encephalitis

Richard Wennberg *, Claude Steriade, Robert Chen, Danielle Andrade

Krembil Neuroscience Centre, University of Toronto, University Health Network, Toronto Western Hospital, Toronto, Canada

ARTICLE INFO

Article history:
Accepted 12 October 2017
Available online 28 October 2017

Keywords:
Autoimmune
DC shift
EEG
Epilepsy
Faciobrachial dystonic seizures

HIGHLIGHTS

- Lateralized muscular spasms ("faciobrachial dystonic seizures") are unique to anti-LGI1 encephalitis.
- Motor spasms are preceded by frontal lobe infraslow activity (ISA) and an electrodecremental pattern.
- ISA heralds the onset of the spasms by ~1.2 s and precedes the electrodecremental pattern by ~700 ms.

ABSTRACT

Objective: The clinical and electrographic features of seizures in anti-LGI1 encephalitis are distinct from those seen in other autoimmune encephalitides or non-encephalitic epilepsies. One electroclinical phenomenon specific to the condition consists of lateralized motor spasms, known as faciobrachial dystonic seizures (FBDS). An electrodecremental pattern overriding a "DC shift" has been described as the EEG correlate of these spasms. We sought to further characterize this pre-spasm infraslow activity (ISA).
Methods: Continuous video-EEG recordings were acquired in four patients with anti-LGI1 encephalitis: each had frequent motor spasms/FBDS as well as frequent subclinical temporal lobe seizures (an independent indicator of anti-LGI1 encephalitis).
Results: In artifact-free recordings obtained using clinical amplifiers equipped with a low frequency analog filter of 0.07 Hz, ISA reliably preceded clinical onset of the motor spasms by ~1.2 s and preceded the electrodecremental pattern by ~700 ms. Pre-spasm ISA was invariably recorded contralateral to FBDS, with a voltage topographic maximum over the mid frontal region. The pre-movement ISA differed from the Bereitschaftspotential in timing and topography and was an order of magnitude higher in amplitude. Sporadic FBDS that occurred in association with temporal lobe seizures were preceded by identical ISA.
Conclusions: The motor spasms of anti-LGI1 encephalitis are preceded by frontal ISA. A paucity of data at the microscale level precludes mechanistic explanations at the macroscale level, or even determination of the relative contributions of neurons and glia in the generation of the ISA.
Significance: Although fundamental cellular mechanisms await elucidation, the pre-spasm ISA represents a singular and readily identifiable EEG response to this autoimmune brain disorder.

1. Introduction

The clinical and electrographic features of seizures in anti-LGI1 encephalitis are distinct from those seen in other autoimmune encephalitides or non-encephalitic epilepsies. The recognition of unusual lateralized motor spasms, which have come to be known as faciobrachial dystonic seizures (FBDS) (Irani et al., 2011a), has greatly facilitated early clinical diagnosis of the condition. Electrographically, a pattern of unusually frequent subclinical temporal lobe seizures in the absence of interictal spikes has been identified as an independent diagnostic marker (Andrade et al., 2011a,b; Steriade et al., 2016).

Brief (~500 ms) generalized attenuation or an "electrodecremental pattern" was first described as the ictal EEG correlate of the motor spasms/FBDS characteristic of anti-LGI1 encephalitis (Andrade et al., 2011a) and used as an argument to support a cortical, epileptic – as opposed to subcortical, non-epileptic – origin for the unusual events. The electrodecremental pattern, typical of tonic seizures, was interpreted as consistent with the initial tonic

* Corresponding author at: Division of Neurology, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario M5T 2S8, Canada.
E-mail address: r.wennberg@utoronto.ca (R. Wennberg).

https://doi.org/10.1016/j.clinph.2017.10.014
1388-2457/

component of the motor spasms and the events were thus described as tonic seizures by Andrade et al. (2011a,b). The prominent, more sustained dystonic component of the spasms was emphasized by Irani et al. (2011a) in their formulation of the FBDS terminology, which was intended to help clinicians identify the syndrome (Irani et al., 2011a,b). More recently, the same motor spasms have been labelled tonic-dystonic seizures (TDS) by Navarro et al. (2016), who described a frontal EEG slow wave preceding contralateral motor spasms by ~580 ms, and further argued for a cortical origin of the clinical events. Relatedly, it had previously been shown that, in addition to the electrodecremental EEG pattern, motor spasms in anti-LGI1 encephalitis were preceded by a "DC shift" visible at standard clinical EEG filter settings (Andrade et al., 2011b), likely representing the same slow wave phenomenon described by Navarro et al. (2016).

DC shifts have been associated experimentally with increased high frequency neuronal activity, the latter marked by amplitude attenuation in typical EEG band-pass ranges, e.g., 1–100 Hz (Gumnit and Takahashi, 1965; Caspers and Speckmann, 1969; Speckmann and Elger, 1993), and a relationship between DC shifts and the EEG electrodecremental pattern has been described in clinical recordings (Ikeda et al., 1997, 1999; Constantino and Rodin, 2012; Gnatkovsky et al., 2014). Focal DC shifts have been demonstrated to herald ictal onsets and high frequency low amplitude oscillations in intracranial recordings in patients with intractable epilepsy (Ikeda et al., 1996, 1999; Bragin et al., 2005; Hughes et al., 2005; Rodin and Modur, 2008; Kim et al., 2009; Rampp and Stefan, 2012; Gnatkovsky et al., 2014; Wu et al., 2014; Kanazawa et al., 2015; Thompson et al., 2016) and regional DC shifts have been shown to correlate with frontal, parietal, temporal and generalized seizures in scalp EEG recordings (Chatrian et al., 1968; Ikeda et al., 1997, 1999; Vanhatalo et al., 2003; Hughes et al., 2005; Rodin et al., 2008).

Given that typical clinical recordings are acquired using AC amplifiers, it has been suggested that the DC shift terminology be replaced in clinical reports by a more accurate descriptor, such as infraslow activity (ISA) (Rodin and Funke, 2012; Thompson et al., 2016), and ISA will be used henceforth in this clinical paper to refer to the DC shift phenomenon.

In the current study, we present a detailed EEG analysis of the previously identified motor spasm-associated ISA (Andrade et al., 2011b), and confirm the pattern to be a reliable marker of FBDS/TDS in anti-LGI1 encephalitis, the ISA appearing maximal over the frontal lobes before clinical onset of the motor events. Potential pathophysiologic mechanisms are explored by comparing ISA topography and lateralization of FBDS, and by examining instances of temporal overlap between FBDS/ISA and the topographically distinct subclinical temporal lobe seizures. In consideration of the debate surrounding cortical versus subcortical and epileptic versus non-epileptic localization and classification of FBDS/TDS (Striano et al., 2011; Boesebeck et al., 2013; Navarro et al., 2016), the ISA is also contrasted with non-epileptiform movement-related cortical potentials (MRCPs), as the pre-spasm ISA bears some resemblance to the late segment (NS′) of the Bereitschaftspotential (BP) (Shibasaki and Hallett, 2006), albeit earlier in onset, topographically distinct, and higher in amplitude.

2. Methods

2.1. Participants

Four patients with anti-LGI1 encephalitis investigated with continuous video-EEG recordings obtained in the Epilepsy Monitoring Unit (EMU) of the Toronto Western Hospital. Three of the patients (women aged 80, 46 and 72 years at illness onset) were studied in the EMU between 2008 and 2010 to guide clinical diagnosis: videos and brief descriptions of their motor movements and standard EEG findings have been published previously (Andrade et al., 2011a). EMU recordings were obtained approximately six, eight and 12 months, respectively, after clinical onsets in these three patients, each of whom began to experience what would now be called FBDS either at or within weeks of clinical onset. The first patient initially presented with mild memory problems and personality changes, the second patient with just the abnormal motor movements, and the third patient presented initially with hyponatremia and a generalized tonic-clonic seizure. Although the second (46-year-old) patient was observed to have typical FBDS, her main motor movements consisted of what could best be described as tonic flexion spasms, involving sudden involuntary flexion at the hips and knees, often with abduction at the shoulders. In the EMU, she occasionally experienced an aura of bilateral foot paraesthesiae lasting a second or more – long enough to activate the event marker and say "I'm going to have one" – before the abrupt onset of hip and knee flexion captured on the video recordings. A majority of her events consisted of just the bilateral flexion spasms, whereas a minority (~30%) started as flexion spasms and ended as lateralized FBDS or, least frequently (~10%), consisted of typical FBDS (in her case inevitably lateralized to the left side of her body). All three patients tested positive for LGI1 antibodies: two ultimately achieved sustained benefit from immunomodulation therapy (mainly repeated courses of IVIg), whereas the 46-year-old patient responded well to treatment with phenytoin and levetiracetam, with disappearance of the motor spasms and no other symptoms. In the latter case, after discussion with the patient a decision was taken to forego immunotherapy: seizures have not recurred during 9 years of follow-up.

The fourth patient, aged 69 years, was investigated in the EMU in 2017, approximately six months after clinical onset with behavioral changes and FBDS. She was treated early in her course with IVIg for a presumptive diagnosis of anti-LGI1 encephalitis, with beneficial response, although test results for LGI1 (and other antineuronal autoantibodies) were negative. Symptoms and signs recurred and she was then admitted to the EMU to look for the presence of the subclinical temporal EEG seizure pattern of anti-LGI1 encephalitis (Steriade et al., 2016) to further support the clinical diagnosis, and to undergo repeat testing for LGI1 antibodies. In addition to dozens of FBDS, multiple bilateral independent temporal lobe seizures were recorded during her 48-h EMU admission; repeat testing was positive for LGI1 antibodies. Initiation of lacosamide and further immunotherapy with steroids and IVIg was of marked benefit, although not in a sustained fashion. Rituximab was recently commenced.

Institutional research ethics board approval was obtained for study of EEG in antibody-mediated encephalitides, and written informed consent obtained from all patients.

2.2. EEG recordings

EEG recordings were obtained using Natus/Xltek (Oakville, Ontario, Canada) EMU40 AC amplifiers, with a sampling frequency of 256 Hz, analog bandwidth of 0.07–100 Hz, and input impedance >100 mΩ. Recordings included 27 EEG electrodes (standard 10–20 plus F9/F10, T9/T10, P9/P10, and surface sphenoidal Sp1/Sp2), two extraoculogram electrodes EOG1/EOG2 and an EKG lead. Although the ISA presented in this paper can be appreciated in bipolar montages (Andrade et al., 2011a,b), referential derivations depict the development and topographic distribution of the slow potentials to advantage, and the data are here presented using either a common average or a linked ears (A1–A2) reference.

One 24-h recording was selected for analysis from each patient, the recording chosen based on an optimal combination of low