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Letter to the Editor

Hippocampal sharp wave ripples during invasive monitoring: A physiologic finding

A 24-year-old, ex 24-week gestational age, high functioning male software engineer, with a seven-month history of poor attention, poor sleep, near-daily headaches, and five discrete 10 to 30-minute episodes of altered mood and disinhibition, was admitted to the epilepsy monitoring unit for a diagnostic evaluation. Four months prior to presentation, he developed a 10-min episode of sudden onset right hemi-body (face, arm, and leg) numbness and weakness, associated with severe headache and nausea. At that time, he was found to have incidental colpocephaly on brain MRI related to his extreme prematurity complicated by neonatal intraventricular hemorrhage, but no other vascular or parenchymal pathology was identified on structural or diffusion MRI or CT-angiography. He was started on amitriptyline as an outpatient, which improved his headache frequency from daily to 2–3 times per week, and he had no further sensorimotor episodes. He continued to complain of disrupted sleep, inattention, and episodes of disinhibited behaviors. A routine EEG was obtained, which identified independent bilateral temporal delta slowing. He was started on levetiracetam 750 mg twice daily for six weeks without symptomatic improvement and was tapered off prior to his admission. During his six-day inpatient video EEG, intermittent independent bitemporal delta slowing was again observed. Invasive foramen ovale electrodes were placed to rule out scalp negative mesial temporal electrographic seizures and did not identify a correlate to the temporal slowing observed on the scalp. This slowing was ultimately attributed to rhythmic mid-temporal theta of drowsiness, given his history of disrupted sleep. Incidentally, on foramen ovale electrode recording, he was found to have abundant bilateral independent hippocampal sharp-wave discharges during non-rapid eye movement (NREM) sleep that coincided with ~ 80 Hz ripple oscillations (Fig. 1). Brain PET imaging was unremarkable. A 40 mg/kg IV valproic acid trial was given without impact on the sharp-wave discharges or the patient's symptoms. Formal neuropsychological testing did not identify mesial or lateral temporal dysfunction but revealed only non-specific mild relative weaknesses in frontal executive functions. The case was discussed among providers, and debate ensued over whether the hippocampal sharp waves represented physiologic or pathologic activity.

There are several validated scoring systems to identify pathologic interictal epileptiform discharges (IEDs), the most widely used being the International Federation of Clinical Neurophysiology (IFCN) criteria (Kane et al., 2017). These criteria include the presence of a: (a) di- or tri-phasic wave with pointed peak; (b) different wave duration than the ongoing background activity; (c) asymmetry of the waveform; (d) after-going slow-wave; (e) disruption of the background; and (f) voltage map with distribution of the negative and positive potentials suggesting a source in the brain corresponding to a radial, oblique, or tangential orientation of the source. IEDs are sensitive biomarkers for epilepsy (Engel, 2011). IEDs activated by NREM sleep could potentially indicate an epileptic encephalopathy, a developmental, electroclinical syndrome in which near-continuous NREM sleep-activated IEDs coincide with cognitive regression. In epileptic encephalopathies, cognitive regressions can be subtle or profound and may require formal neuropsychological testing to detect (Wickens et al., 2017).

Several physiologic sharp waves during drowsiness or sleep, well-characterized on the scalp EEG, were considered and ruled out. In the temporal regions, these include wickets – rhythmic 6–11 Hz waves with an arciform appearance, maximal in the mid-temporal regions, observed in drowsiness and light sleep, and benign epileptiform transients of sleep (BETS) – small (<50 μV), brief (<50 ms), diphasic sharp spikes in the temporal region with a broad field in drowsiness and light sleep, also known as small sharp spikes (SSS). Extratemporally, classic physiologic sharp waves of sleep also include vertex waves – sharp waves maximal at the vertex during NREM sleep, and positive occipital sharp transients of sleep (POSTS) – triangular shaped waves that originate in the occipital region during light and NREM sleep (Britton et al., 2016; Asadi-Pooya and Sperling, 2019). Unlike pathologic IEDs, these physiologic sharp waves disappear in N3, do not disrupt the background, and do not have a prominent slow wave.

In this case, given the patient's nonspecific clinical symptoms, the lack of response to anticonvulsant medication treatment, the absence of seizures, the normal mesial temporal MRI and PET imaging findings, and normal mesial temporal neuropsychological function, the clinical team ultimately concluded that the sharp waves observed were not pathologic epileptiform discharges. However, most members of the neurophysiology team were not familiar with the well-characterized physiologic waveform that best matched the observed activity: the hippocampal-sharp wave ripple (HC-SWR).

HC-SWRs are physiologic sharp waves activated during NREM sleep and are considered essential for normal sleep-dependent memory consolidation (Buzsáki, 2015). HC-SWRs occur when neurons replay wakeful firing patterns and are specific to the hippocampus. These sharp events are only evident on invasive hippocampal recordings with a high enough sampling rate to detect the concurrent gamma band ripple activity (typically requiring sampling rates > 500 Hz) (Chu et al., 2017). Morpholog-

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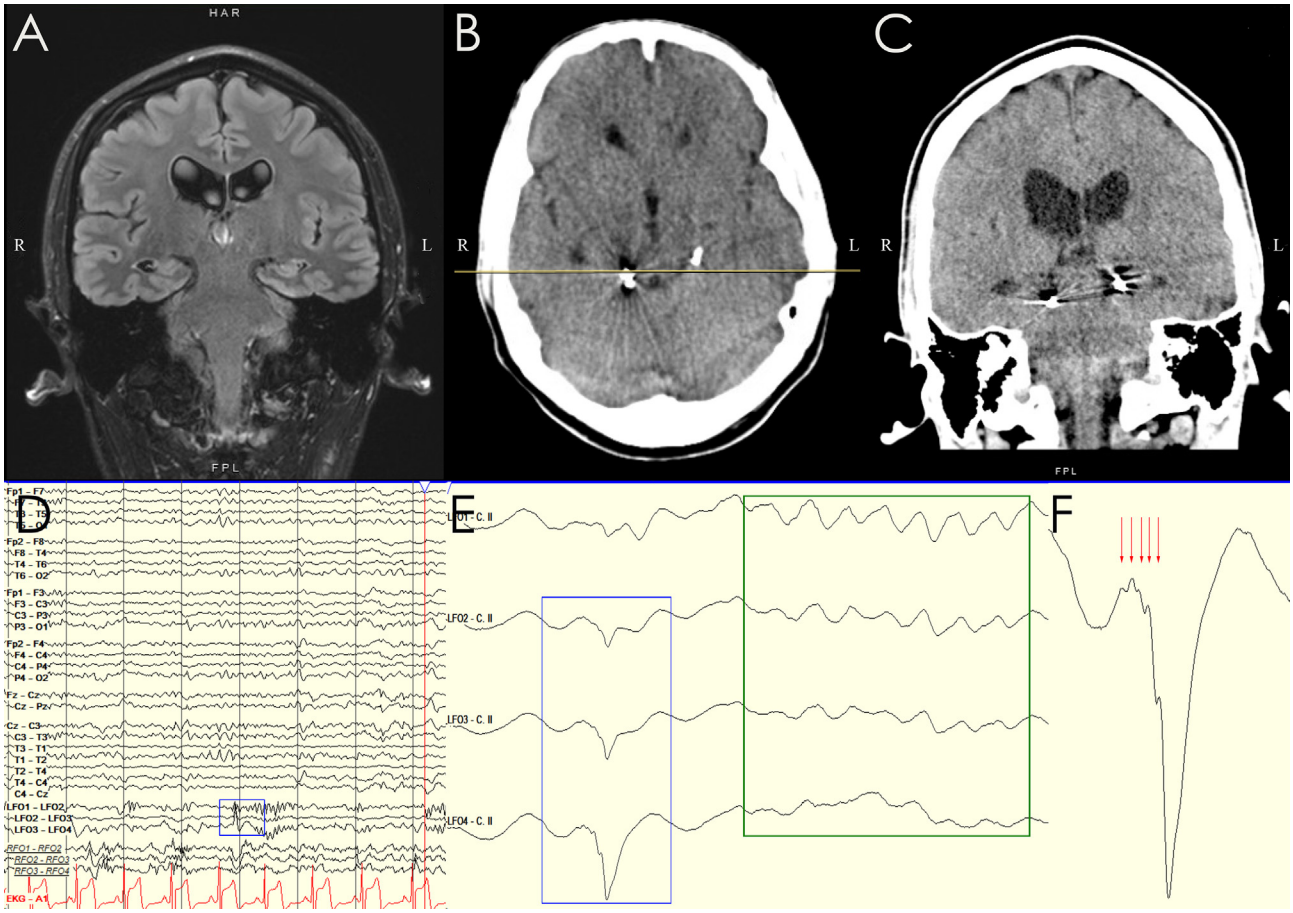

Fig. 1. Example hippocampal sharp wave ripple from our patient. (A) 3T MRI revealed incidental colpocephaly and symmetric bilateral hippocampi with normal architecture and signal intensity on FLAIR sequence in the coronal view. (B-C) Computer tomography with placement of bilateral foramen ovale electrodes in axial and coronal views, showing contact 3 on the left and contact 1 on the right, approximating mesial temporal structures. (D) Example of sharp activity (blue box) observed in bilateral foramen ovale electrodes during non-rapid eye movement sleep (bipolar montage). (E) Close up of the left foramen ovale contacts (referential montage with CS2 reference) shows an example sharp wave maximal in LFO4 (blue box) preceding a 14 Hz sleep spindle oscillation maximal in LFO1 (green box). (F) Further close-up of LFO4 recording reveals ripple oscillations (red arrows, 75–85 Hz) over-riding the hippocampal sharp wave, consistent with a hippocampal sharp wave ripple. Data was sampled at 1035 Hz and high-pass filtered at 1 Hz. R = right hemisphere; L = left hemisphere. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ically, they are characterized by a large, negative, ~50–100 ms sharp wave with superimposed 80–200 Hz "ripple" band activity, followed by a ~ 200 ms positive delta-wave. They commonly follow theta bursts and precede sleep spindles (Jiang et al., 2019). The invasive EEG recordings in our case fully matched these criteria Fig. 1. While much of the research on HC-SWRs has been in animals, recent data illustrates that HC-SWRs co-occur with distant cortical sleep waves and in all stages of NREM sleep in humans. They are rare to absent in wakefulness, occur more frequently in stage 3 NREM than stage 2 NREM sleep, and may occur at higher frequencies in the anterior hippocampus compared to posterior hippocampus (Jiang et al., 2020). Because they may be indistinguishable from IEDs based on available criteria, familiarity with this waveform is essential to avoid false positive interpretations of epileptiform activity.

As minimally invasive stereo-EEG recording techniques become more widely available (Gavvala et al., 2020), epileptologists must coincidentally expand their lexicon of normal electrophysiology to include the HC-SWR. This graphoelement should be included in the differential of bilateral independent sleep-activated sharp wave activity confined to the hippocampus, particularly in the absence of seizures. Recording invasive data at higher sampling rates may help identify these unique graphoelements. Misinterpretation of normal physiology as epileptiform can have damaging clinical consequences with potentially unnecessary treatment or surgical intervention (Benbadis and Lin, 2008). Recognition of normal variants of both scalp and intracranial recordings will help avoid these pitfalls.

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Declaration of Competing Interest

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