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Anatomical and physiological basis of continuous spike–wave of sleep syndrome after early thalamic lesions

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ABSTRACT

Objective: Early neonatal thalamic lesions account for about 14% of continuous spike–wave of sleep (CSWS) syndrome, representing the most common etiology in this epileptic encephalopathy in children, and promise useful insights into the pathophysiology of the disease.
Methods: We describe nine patients with unilateral neonatal thalamic lesions which progressed to CSWS. Longitudinal whole-night and high-density electroencephalograms (EEGs) were performed, as well as detailed imaging and clinical evaluation. Visual evoked potentials were used to probe cortical excitability.
Results: Thalamic volume loss ranged from 19% to 94%, predominantly on medial and dorsal nuclei and sparing the ventral thalamus. Lesions produced white matter loss and ventricle enlargement on the same hemisphere, which in four patients was associated with selective loss of thalamic-cortical fibers. Cortical thickness quantification failed to reveal hemispheric asymmetries. Impact on EEG rhythms was mild, with a volume-loss-related decrease in alpha power and preservation of sleep spindles. The sleep continuous spiking was lateralized to the hemisphere with the lesion. Visual cortex stimulation in five patients with posterior cortex spiking revealed an abnormal frequency-dependent excitability at 10–20 Hz on the side of the lesion.
Significance: Unilateral selective thalamic-cortical disconnection is a common feature in our patients and is associated with both a focal pattern of CSWS and a pathological type of frequency-dependent excitability (peak: 10–20 Hz). We propose that this excitability represents an abnormal synaptic plasticity previously described as the augmenting response. This synaptic plasticity has been described as absent in the corticocortical interactions in healthy experimental animals, emerging after ablation of the thalamus and producing a frequency-dependent potentiation with a peak at 10–20 Hz. Because this response is potentiated by sleep states of reduced brainstem activation and by appropriate stimulating rhythms, such as sleep spindles, the simultaneous occurrence of these two factors in nonrapid-eye-movement sleep is proposed as an explanation for CSWS in our patients.

1. Introduction

The syndrome of continuous spike–wave of sleep (CSWS) is an important treatable epileptic encephalopathy with peculiar features that set it apart from the seizure-related morbidity associated with other types of epilepsies [1]. Retrospectively, the first examples clearly identifiable as CSWS were reported [2] in six children. The peculiar appearance of continuous spiking with sleep onset, the fast disappearance with both rapid eye movement (REM) and waking, and the persistent occurrence "night after night" for years were all described in this early report. More recently, the syndrome was reclassified as an age-related and self-limited childhood encephalopathy [3]. An incidence of neuroradiological abnormalities in between 33% and 60% of cases with CSWS have been reported in several series [4], with lesions dominated by unilateral or diffuse atrophy, but cases of porencephaly, pachygyria,

Abbreviations: CSWS, continuous spike–wave of sleep; VPS, ventricle-peritoneal shunt; HR-EEG, high-resolution electroencephalogram; DWI, diffusion weighted imaging; Thal-Bundle, thalamic bundle; SSVEPs, steady-state visual evoked potentials; SNR, signal–noise ratio; sLORETA, standard low-resolution tomography.

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cortical developmental disorders, polymicrogyria, and hydrocephalus have also been reported. A more recent list [5] adds yet other lesions but, most importantly, highlights the importance of early vascular thalamic lesions.

The connection between early thalamic lesions and CSWS was first suggested in case reports [6–8]. A large series ($N = 32$) of patients with early thalamic lesions strengthened the case for this connection [9] by demonstrating that 37.5% of patients with early thalamic lesions presented the syndrome years later. An enlarged series from the same group with $N = 60$ patients [10] and a more careful prospective study of the new cases revealed that patients with thalamic lesions involving predominantly mediodorsal nuclei had a higher probability of evolving to CSWS. Kersbergen et al. [11] followed prospectively 14 survivors of early thalamic hemorrhages and found CSWS-like (spike index > 50%) in 5, sleep-induced epileptiform activity in 2, and focal epilepsy in another 2. The young age of some of the patients, below the typical age of onset of CSWS, suggests that these numbers are lower estimates, and yet they support a relationship between the two pathologies. The relative importance of this etiology in the common CSWS of the general population was addressed in a group of $N = 100$ children [5] with a CSWS-like clinical presentation and spike index higher than 50% in which 14% had evidence for thalamic lesions, the single most important etiology.

In the present study, we characterize the neurophysiological features of CSWS in a group of patients with neonatal thalamic lesions and propose an anatomical and physiological model for the origin of the associated sleep-related continuous spiking.

2. Methods

2.1. Clinical data

Clinical data for the nine patients in the present series are shown in Table 1. Patients were selected from a population of children with CSWS evaluated at the clinical neurophysiology laboratory of the first author in the time span of 15 years, with the additional requirement that a well-defined thalamic lesion was identified in the magnetic resonance imaging (MRI) study. Cases with diffuse encephalopathy, hypoxic-ischemic etiology, or structural lesions extending beyond the thalamus were excluded.

In all patients, the lesion was unilateral, and seven out of nine had a clear history of neonatal thalamic hemorrhage, with an acute severe brain disease which in two cases required the placement of a ventricle-peritoneal shunt (VPS) (Fig. 4B). Of the patients with no history of thalamic hemorrhage, one had no pathological events preceding the epilepsy onset and consequent MRI diagnosis (patient 2), whereas in the other case (patient 5), preeclampsia was diagnosed in the late stages of pregnancy and the posterior MRI showed thalamic deposition of hemosiderin supporting a previous hemorrhagic event (Supplementary Fig. 1).

Most patients suffering thalamic hemorrhage recovered surprisingly well, and four out of seven met the early motor and cognitive developmental milestones, (Table 1). In three patients, this development was delayed, which in two cases was partially attributed to surgical complications associated with the management of the hydrocephalus.

In most patients, the later onset of CSWS was associated with significant deterioration of behavioral and cognitive capabilities (Table 1).

2.2. Electroencephalogram (EEG) acquisition and processing

All patients were submitted to repeated whole-night EEG recordings using the 10–20 system plus subtemporal electrodes (F9/10 and P9/10) and quantification of the Spike Index (SI) using a modification of the method of Larsson et al. [12], with determination of the ratio of 3-s epochs with spikes and without spikes in an integration time of 30 s (instead of the 10-min period in the original method), running through the whole EEG trace. With this modification, we could perform a quantification of the SI for each sleep stage evaluation. Patient P8 had a whole-night recording only after CSWS resolution and clearing of the EEG spikes, so an SI quantification was not possible.

A high-resolution electroencephalogram (HR-EEG) was performed in eight of the nine patients. This consisted of 1- to 2-h recordings using a cap (EasyCap Inc) with 82 electrodes, corresponding to the full 10–10 system plus electrodes F11/12, FT11/12, TP11/12, and P11/12, and electrocardiogram. A digital EEG amplifier was used (SynAmps2, Compumedics-Neuroscan), with sintered AgCl ring electrodes, a sampling rate of 1000 Hz, and filters DC 70 Hz. The first part of the recording included resting-state and visual evoked potentials, whereas the second part included a 30-min nap. Localization of the spike activity of CSWS was performed using a realistic boundary element model (BEM), obtained from segmentation of the anatomical T1 sequence for each patient. Scalp maps of the average and Laplacian representative spike at half-peak and peak amplitude were computed along with source analysis using the cortical standard low-resolution tomography (sLORETA) model implemented in the CURRY6.0 software (Compumedics-Neuroscan). In one patient, we could not obtain the Laplacian because he did not cooperate to obtain an acceptable HR-EEG.

The posterior alpha and mu spectral data were obtained from the HR-EEG at rest with eyes closed and eyes open, respectively. The average spectra of several (15 to 20) 1-s epochs for each channel (applying a Hanning window and fast Fourier transform [FFT]) were computed and used to draw a scalp representation map of the power distribution. The interhemispheric ratio was computed from the power in electrodes C3/4 for Mu and the average power of electrodes P7/8, CP3/4, and O1/2 for the posterior alpha. Spindles were manually located in the Cz channel of whole-night EEG recordings, and 30–50 1-s epochs were obtained and used to compute the average spectra for each channel. With these spectra, we compared hemispheres (using the C3-F7 and C4-F8 derivations) and obtained a global map of power distribution at the peak of spindles. The asymmetry index (AI) was computed as $AI = (P - N) / (P + N)^*100$, where P and N are the power in pathological and normal hemispheres [13].

The correlation between SI and the sleep stage was obtained by manually scoring the whole-night EEG recordings using EEG derivations from the nonlesioned hemisphere. For each sleep stage, we computed the average SI for the whole night.

2.3. Imaging of and volumetry data

In all patients, an anatomical whole-brain MRI was obtained, which allowed manual volume quantification of the whole thalamus, using the methodology described in Power et al. [14] and pulvinar using the guidelines of Byne et al. [15]. Because lesions were always unilateral, volumes were normalized to the healthy hemisphere. In six patients, automatic quantification of the cortical thickness using the software FreeSurfer was performed. In order to compare diverse cortical areas, the cortical reconstruction of each hemisphere was automatically parceled into the 74 areas of the Destrieux atlas, and the average cortical thickness of each area was compared between hemispheres.

In four patients, diffusion-weighted imaging (DWI) was obtained using the following parameters: spin-echo echo-planar imaging sequence with $b = 1000$ s/mm^2, 25 directions, 1 non-DWI image, resolution $= 4.0 \times 4.0 \times 4.0$ mm^3, 36 slices with no gap, and echo time/repetition time of 89.7/8475 ms. Deterministic tractography quantification of the structural connectivity between the thalamus and temporal lobes and also of the pyramidal pathway was performed (Fig. 5A) after standard preprocessing steps, including Eddy current distortion, with the freely available software tool DiffusionKit (http://diffusionkit.readthedocs.io) [16]. After fiber reconstruction using the manually segmented thalamus as seed and excluding vertically and posteriorly projecting bundles using appropriate exclusion planes (Fig. 5A, left), we identified the two most important bundles projecting to the

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