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Reduced thalamic volume in patients with Electrical Status Epilepticus in Sleep

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ABSTRACT

Purpose: To test whether patients with Electrical Status Epilepticus in Sleep (ESES) and normal neuroimaging have a smaller thalamic volume than expected for age and for total brain volume.
Methods: Case-control study comparing three groups of subjects of 4–14 years of age and normal magnetic resonance imaging: 1) ESES patients, 2) patients with refractory epilepsy control group, and 3) healthy controls. Thalamic and total brain volumes were calculated using an algorithm for automatic segmentation and parcellation of magnetic resonance imaging.
Results: Eighteen ESES patients, 29 refractory epilepsy controls and 51 healthy controls were included. The median (p25–p75) age was 8.8 (7.5–10.3) years for ESES patients, 11 (7–12) years for healthy controls, and 9 (6.3–11.2) years for refractory epilepsy controls. After correcting for total brain volume and age, the left thalamus was not statistically significantly smaller in ESES patients than in healthy controls ($p = 0.077$), in ESES patients than in refractory epilepsy controls ($p = 0.056$); but the right thalamus was smaller in ESES patients than in healthy controls ($p = 0.044$), and in ESES patients than in refractory epilepsy controls ($p = 0.033$).
Conclusion: Patients with ESES and normal magnetic resonance imaging have smaller relative thalamic volume controlling for age and total brain volume.

1. Introduction

Electrical status epilepticus in sleep (ESES) is an electroencephalogram (EEG) pattern characterized by infrequent epileptiform discharges during wakefulness that become markedly potentiated during sleep leading to continuous or almost continuous spikes and waves during non-rapid eye movement (non-REM) sleep (Nickels and Wirrell, 2008; Sánchez Fernández et al., 2012a; Tassinari et al., 2000). ESES is found in several electro-clinical syndromes which present three main features with different degrees of severity: sleep-potentiated epileptiform activity (ESES and related EEG patterns), seizures, and developmental regression, including Continuous Spike and Wave during Slow Wave Sleep and Landau-Kleffner Syndrome (Nickels and Wirrell, 2008; Panayiotopoulos et al., 2008; Sánchez Fernández et al., 2012a; Tassinari et al., 2000).

The underlying pathophysiology leading to ESES and its accompanying features is complex and only partially understood. In animal models, disruptions in the neurotransmission of the cortico-thalamo-cortical spindle-generating circuitry lead to generalized spike-waves, similar to those found in ESES (Beenhakker and Huguenard, 2009). It has been hypothesized that an early developmental thalamic lesion may disrupt thalamic neurotransmission leading to ESES (Beenhakker and Huguenard, 2009; Guzzetta et al., 2005). Several series have shown the association between early developmental thalamic lesions, especially of vascular etiology, and ESES or related EEG patterns (Guzzetta et al., 2005; Incorpora

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Table 1
Demographic and clinical characteristics of the study population.

	ESES patients N = 18		Healthy controls N = 51	Refractory epilepsy controls N = 29	
Age at MRI (in years)					
Mean (SD)	9 (2.6)		10 (2.9)	8.6 (2.9)	
Median (p25-p75)	8.8 (7.5–10.3)		11 (7–12)	9 (6.3–11.2)	
Minimum-Maximum	4.6–14		5–14	4–13.2	
Gender					
Male	12 (66.7%)		28 (54.9%)	15 (51.7%)	
Female	6 (33.3%)		23 (45.1%)	14 (48.3%)	
Incidental findings on MRI (MRI considered within normal limits)					
Pineal cyst	1		0	3	
Questionable non-specific hippocampal variants classified within normal limits	1		0	3	
Non-specific foci of T2 hyperintensity	2		0	5	
Mild prominence of the periaxial spaces and ventricular system	1		0	2	
No incidental findings	13		51	16	
Epilepsy classification		Predominant side of discharges	Not applicable		Predominant side of discharges
CSWS	12	9 B, 1R, 2L		0	0
LKS	3	2R, 1L		0	0
Difficult-to-control epilepsy non-otherwise specified	3	3B		19	5B, 7 M, 3L, 4R
Lennox-Gastaut syndrome	0	0		4	1B, 3 M
Dravet syndrome	0	0		1	1 M
Doose syndrome	0	0		1	1 M
Refractory temporal lobe epilepsy	0	0		3	2L, 1R
Refractory frontal lobe epilepsy	0	0		1	1R
Medication		Not applicable			
Conventional AEDs					
Mean (SD)	2.7 (1.2)			4.3 (1.5)	
Median (p25-p75)	3 (2–3)			4 (3–5)	
Minimum-Maximum	0–4			2–9	
High-dose benzodiazepines	4			0	
Corticosteroids/ACTH	1			3	
Intravenous immunoglobulin	0			1	
Ketogenic diet	0			5	
Type of MRI[a]					
1.5T	11		34	18	
3T	7		17	11	

Legend: ACTH: Adrenocorticotrophic hormone. **AED:** Antiepileptic drug. **B:** Bilateral. **CSWS:** Continuous spikes and waves during sleep. **ESES:** Electrical Status Epilepticus in Sleep. **L:** Left. **LKS:** Landau-Kleffner syndrome. **M:** Multifocal. **MRI:** Magnetic resonance imaging. **R:** Right. **SD:** Standard deviation. **p25:**25th percentile. **p75:** 75th percentile. Differences in age were not statistically significantly different (Kruskal-Wallis test, $p = 0.0894$). **T:** Tesla.

[a] The distribution of 1.5T and 3T MRI scans was not statistically significantly different with a chi-square test $p = 0.875$.

et al., 1999; Kelemen et al., 2006; Kersbergen et al., 2013; Monteiro et al., 2001; Sánchez Fernández et al., 2012c). In a series of 32 patients with prenatal or perinatal thalamic lesion, prominent sleep potentiation of epileptiform activity occurred in 29 (90.6%) patients (Guzzetta et al., 2005) and in a series of 14 survivors of perinatal thalamic hemorrhage, seven (50%) developed ESES or related EEG patterns during childhood (Kersbergen et al., 2013). Early developmental thalamic lesions are specifically associated with ESES, with thalamic lesions 7.5 times more frequent in patients with ESES than in patients with other types of epilepsy (Sánchez Fernández et al., 2012c). In spite of this strong association, thalamic lesions are found in only approximately 14% of patients with ESES (Sánchez Fernández et al., 2012c) and structural brain lesions in any brain area in less than half of patients with ESES. Most patients have a normal magnetic resonance imaging (MRI) and their underlying etiology remains unknown.

This study aimed to address this gap. Our working hypothesis is that patients with ESES and normal MRI may have had minor early developmental thalamic lesions or dysfunction not severe enough to be visible on MRI but sufficient to alter the neurotransmission of the cortico-thalamo-cortical circuitry and cause a small decrease in thalamic volume. This study tested the hypotheses of whether patients with ESES have a smaller thalamic volume than i) a group of healthy controls and ii) a group of controls with refractory epilepsy without ESES.

2. Patients and methods

2.1. Protocol approval

This study was approved by the Institutional Review Board of Boston Children's Hospital

2.2. Study design

We performed a case-control study at a tertiary pediatric epilepsy center

2.3. ESES patients

ESES patients were consecutive patients who met the following inclusion criteria: 1) presence of the ESES pattern on at least one overnight EEG recording, defined as spikes and waves occupying ≥50% of the non-REM sleep tracing, 2) MRIs classified within normal limits for age, 3) at least one MRI of sufficient technical quality to perform volumetric analysis, and 4) age 4–14 years at the time of