

High incidence of early thalamic lesions in the Continuous Spike-Wave related with slow Sleep (CSWS)

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ABSTRACT

Objective: Continuous Spike-Wave during slow Sleep (CSWS) syndrome associates a clinically important neurocognitive regression with strong activation of non-REM sleep spikes. Its mechanisms remain unknown, but a contribution of rare perinatal thalamic injuries has been highlighted. We determine the incidence of such lesions in a cohort of CSWS patients.

Methods: N = 65 patients with CSWS and a control group (N = 51) were studied. Spikes were quantified in long-term ambulatory EEGs, brain Magnetic Resonance Imaging (MRI) structural lesions were assessed and thalamic volumetry was performed. A neurocognitive scale was used to assess dysfunction.

Results: The most common etiologies in the control patients were not represented in the CSWS group. Structural lesions were detected in a minority of CSWS patients (25/53) but included a thalamic injury in the large majority (24/25). This ratio was 4/40 in controls.

Lesions belonged to one of five types: 1. Circumscribed to the thalamus (N = 11); 2. Extending beyond the thalamus (N = 3); 3. Hypothalamic-Hamartomas (N = 4); 4. Periventricular-Leukomalacia (N = 4); 5. Hypoplasia-Polymicrogyria (N = 1).

Most lesions were lateralized to one hemisphere, which in all cases corresponded to the lateralization of the CSWS.

Significance: Thalamic lesions are present in most CSWS patients with abnormal MRIs, supporting an important role in its genesis.

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1. Introduction

The Continuous Spike-Wave related with slow Sleep (CSWS) syndrome is a peculiar condition of childhood first described in the early 70s [1] which associates neurocognitive regression with a striking activation of spikes in the non-REM sleep stages. The persistent association between the non-REM rate of interictal spikes and the neuropsychological impairment, as well as its variation with spontaneous or pharmacologically induced fluctuations, has motivated the development of quantitative techniques to assess risk and response to therapy, (reviewed in [2]). Seizures are not

the main source of disability in most patients and are even absent in some, which has led to the current belief that they play a minor role in functional deterioration [3].

The consistent age-related onset of the condition, the very reliable non-REM sleep spike activation, every night while the condition persists, and the uniform regression by adolescence, suggests that a common mechanism underlies the condition. Despite this suspicion, no widely accepted model has been proposed. Some of the factors which contribute to this difficulty are the absence of structural brain lesions in the MRI of most patients as well as the high diversity of etiologies that have been described in association with the syndrome [4,5]. The peculiar poor response to the typical antiepileptic drugs and relative effectiveness of corticosteroids [6], further point to a distinct underlying mechanism from the one of the common childhood epilepsies.

Among the diverse etiologies, structural lesions of the thalamus have attracted increased attention not only because they provide

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well-defined anatomical lesions with interesting commonalities between patients (reviewed in [7]), but also because they have high predictive power for the future development of the syndrome [8]. In a series of papers ([9;10;11]) we have explored the features of CSWS associated with structural lesions restricted to the thalamus, mostly resulting from hemorrhagic perinatal events, and found an important cortico-cortical disconnection in the hemisphere with the thalamic lesion, associating with the development of Electrical Status Epilepticus of Sleep (ESES) lateralization to the same hemisphere. Overall, thalamic lesions currently appear as an important window of opportunity to probe the brain mechanisms leading to CSWS, as suggested years ago by Monteiro et al [12], and we are approaching the demonstration of a causal relationship between the structural injury and the syndrome.

Despite the promising features of early thalamic injuries as a possible cause of ESES, the fact that these conditions are not frequent in CSWS patients (14% in [4]) rises questions on how generalizable this underlying brain dysfunction is in the syndrome. If it is an important etiology, as we believe, then its incidence in CSWS patients should be much higher than has been reported in the studies currently available. A robust determination of the true incidence of early thalamic lesions in the CSWS syndrome would establish the relative importance of this etiology among a wide range of competing conditions.

Because to the best of our knowledge, no previous research has firmly established the true incidence of the structural thalamic lesion in CSWS cases, in this study we decided to assess the following points:

1. Establish the incidence of thalamic structural injuries in a population of CSWS patients classified with robust neurophysiological criteria.
2. Correlate the hemispheric lateralization of ESES and the thalamic lesions.
3. Correlate the severity of neurocognitive impairment in CSWS patients with and without thalamic lesions.

The evidence for a high degree of association of the CSWS syndrome with the rare early thalamic lesions previously described in the literature [4,7,8,9,12,22] together with the first evidence for a high incidence of such lesions in a series of CSWS patients provided by the present report, support the interpretation that this is the most important etiology of the syndrome identified so far, establishing a common link between a wide range of apparently independent conditions previously described in these patients.

2. Clinical data and methods

2.1. Patient selection

Patients included in the present study were children (aged 3–14 years) referred to the clinical neurophysiology lab of our institution for quantification of spikes in the context of neurocognitive dysfunction with the suspicion of CSWS in the time period from 2008 to 2021. The geographical area of origin of the patients included the south of Portugal and mainly the Lisbon region. All the patients exhibited some degree of acquired neurocognitive dysfunction and had EEG evidence of abundant spikes in routine sleep studies. All the neurophysiological records were obtained for the purpose of clinical diagnosis and monitoring, and retrospectively included in the study, so no specific patient consent was obtained. Despite the fact that most patients had several EEG recordings available, only one per patient was included in the present study, usually, the first one, always performed before any specific therapy for the CSWS syndrome. Patients with seizures were medicated with conventional AEs and the ones with no seizures were medication free. The MRI sequences consisted of stud-

ies performed solely for clinical practice support and were made available by the parents of the patients after an explanation that they could be used for clinical research in the CSWS condition. The study protocol was approved by the ethics committee of CHPL.

Spikes were quantified using methods detailed in 2.2, and patients were classified as CSWS if the average maximal SWI for the first 4 sleep cycles of nocturnal recordings was higher than 50% and the neurocognitive regression was confirmed. An age-matched control group of children with refractory epilepsies, mostly studied in the context of surgery of epilepsy, and patients assessed for but not fulfilling the requirements for CSWS, was organized. Clinical and neurophysiological data for the CSWS and control patients are shown in Table 1 and Table A.1, respectively.

Clinical imaging was available for most CSWS patients (53 out of 65) and in 35 of these an anatomical T1 sequence was available allowing thalamic volumetry, (Table A.2). Most of the patients with no imaging data available were focal self-limited childhood epilepsies (SeLECTS, SeLEAS, COVE) or Landau-Kleffner Syndromes (LKS), Table 1.

2.2. Quantification of spikes

Long-term EEG recordings (10–20 system), including at least 1 hour of wakefulness and the whole night, were used for spike quantification. The general procedure is shown in Fig. 1a: (a) Visual selection of the 4 EEG channels with maximal amplitude of spikes activating in sleep; (b) High-pass filtering with 5 Hz cutoff (FIR); (c) Automatic creation of spike templates using spike clustering software (SPIKE2 from CED Inc.); (d) Visual selection of the appropriate templates by experienced clinical neurophysiologist; (e) Exhaustive spike detection; (f) Quantification of the Spike Wave Index (SWI) in 10 minutes epochs using methods described in [13]; (g) Determination of the CSWS Index [14]; (h) Spike frequency (spikes/min) was also quantified. The control group patients were evaluated with the same methodology.

We used as the main metric for classification the CSWS Index described in a previous publication of our group [14], which averages the peaks of the Spike-Wave Index [13] time course for the first four non-REM night sleep cycles. It spans the range from 0% (no continuous spike-wave peaks) to 100% (fully continuous spike-wave). The classification power of this metric was assessed in comparison with several others extracted from the previous spike quantification, using the area under the curve (AUC) metric from a Receiving Operating Characteristics (ROC) curve (Fig. 1d).

2.3. Quantification of thalamic lesions

The thalamic lesions were classified into five types, (Fig. 2a): 1. Lesions circumscribed to the thalamus; 2. Lesions including but extending beyond the thalamus; 3. Hypothalamic Hamartomas; 4. Thalamic lesions in the context of Peri-Ventricular Leukomalacia (PVL); 5. Thalamic hypoplasia associated with cortical polymicrogyria. The distribution of each type in both the CSWS and control patients is shown in Fig. 2c.

The thalamic volumes in CSWS (N = 35) and control patients (N = 15) with an anatomical 3D sequence available were performed manually using the ITK-SNAP software (<https://www.itksnap.org/>) and the anatomical rules published in [15], (Table A-2).

2.4. Neurocognitive assessment

The neurocognitive assessment was performed retrospectively by the neurologist in charge of EEG reporting as a way of summarizing available evidence on cognitive, behavioral, or neurological disturbances provided by the referring physician or reported by the family of the patient to the neurophysiologist technician at

Table 1
Clinical data (CSWS).

	Sex	Age	Gestation	Perinatal Period	Pregnancy	Epilepsy onset(y)	Etiology group	MRI(Normal = 0)	3D MRI	Lesion(hemisph)	Lesion(lobe)	ESES Hemisph	CSWS Index	Global Score
3	M	8	FT	normal	uneventful	5	Thalamic	1	y	right	thal	right	0.96	3
	F	9	FT	normal		4	SeLECTS	0	y			right	0.89	0
	F	7	FT	normal		3	SeLECTS					right	0.64	2
	F	8	FT	normal		2	CP					left	0.97	2
	M	9	FT	normal		5	Thalamic	1	y	left	thal	left	1.00	3
	F	8	FT	normal		8	SeLECTS	0	y			left	0.95	3
	F	9	FT	Thal Hemorr(D2)	uneventful	7	Thalamic	1	y	left	thal	left	0.91	3
	F	4	FT	normal		ns	LKS	0				left	0.63	2
	M	5	FT	normal		5	SeLECTS					left	0.95	1
	F	11	PT(29w)	Diplegia	uneventful	4	PVL	1	y	right	thal+	right	1.00	4
	M	7	PT(29w)	Caud Hemorr(D1)	twin pregnancy	3	PVL	1	y	left	multiple	left	0.63	3
	M	7				3	SeLECTS	0				right	0.80	3
	M	7	FT	normal		6	SeLECTS	0	y			left	0.70	2
	M	8	FT	HLHS(rh stroke)	uneventful	1	Thalamic + Stroke	1		right	thal+	right	0.92	4
	M	8	FT	normal		5	SeLEAS	0				right	0.98	2
	M	6				5	not classified	0				left	0.97	1
	M	9	FT	normal	preeclampsia	8	SeLECTS	0				right	0.99	3
	M	9	FT	normal		7	LKS	0	y			left	0.88	3
	M	14				4	SeLECTS	0				left	0.93	2
	M	7	FT	normal		7	SeLECTS	0				left	0.94	2
	M	5	FT	normal		1	SeLECTS	0	y			right	0.69	2
	F	3	PT(36w)	normal	uneventful	3	LKS	0				left	0.97	3
	F	4	FT	normal	threatened abortion	2	SeLECTS	0	y			right	0.80	3
	F	7	FT	normal	uneventful	1	Perisylvian polymicrogyria	1		bilateral	perisylvian	right	0.94	4
	M	8	FT	Thal Hemorr(D30)	uneventful	3	Thalamic	1	y	left	thal	left	0.82	2
	M	8	PT(37w)	Thal Hemorr(D9)	placental abruption(37w)	1	Thalamic	1	y	left	thal	left	0.80	4
	M	9	FT	Thal Hemorr(D18)	uneventful	1	Thalamic	1	y	right	thal	right	1.00	4
	F	4	PT(36w)	normal	twin pregnancy	4	LKS	0	y			left	0.80	1
	M	8	FT	normal	uneventful	5	Thalamic	1	y	right	thal	right	1.00	4
	F	8	FT	normal		4	SeLECTS					right	0.76	2
	M	4	FT	normal		ns	LKS	0				left	0.96	3
	F	7	FT	Thal Hemorr(D3)	uneventful	0	Thalamic	1	y	right	thal+	right	0.61	4
	F	12	PT(30w)	Thal Hemorr	uneventful	1	Thalamic	1		left	thal	left	0.87	3
	F	6	FT	normal	uneventful	6	SeLEAS					right	0.80	3
	F	7	FT	normal		ns	SeLECTS	0				bilateral	0.72	2
	F	8	FT	normal	uneventful	3	SeLECTS					bilateral	0.72	3
	F	7	PT(32w)	normal		3	LKS	0	y			left	0.54	4
	F	12	PT(37w)	Thal Hemorr(D30)	uneventful	3	Thalamic	1	y	left	thal	left	1.00	4
	M	5	FT	normal		4	LKS	0	y			left	0.97	4
	M	9	FT	normal		4	SeLECTS					left	0.97	3
	M	4	PT(36w)	normal	uneventful	4	SeLECTS	0				left	0.70	2
	M	5	FT	normal		5	LKS	0	y			left	0.86	3
	M	6	FT	Stroke(MCA)	uneventful	2	Thalamic + Stroke	1		right	thal+	right	0.97	3
	M	7	PT(35w)	normal	threatened abortion	ns	SeLECTS					left	0.97	3
	F	8	FT	normal		2	Thalamic	1	y	right	thal	right	0.88	3
	M	3	PT(34w)	normal	preeclampsia	4	LKS	0	y			left	0.82	4
	M	5	FT	normal	normal	5	SeLECTS					left	0.87	3
	M	4	PT(37w)	normal	normal	3	SeLECTS	0				left	0.58	2
	M	9	FT	normal		4	SeLECTS					right	0.61	
	M	9	FT	normal		1	Hypothalamic Hamartoma	1	y	left	hypothalamus	left	0.78	3
	M	8	FT	normal	normal	0	Hypothalamic Hamartoma	1	y	right	hypothalamus	right	0.78	3
	F	2	PT(35w)	normal	Bleeding 1st trimester	0	Hypothalamic Hamartoma	1	y	right	hypothalamus	right	0.76	3
	M	2	FT	normal	uneventful	0	Hypothalamic Hamartoma	1	y	left	hypothalamus	left	0.78	3
	F	2	PT(37w)	normal	uneventful	0	Thalamic + Stroke	1	y	left	thal+	left	0.80	3

(continued on next page)

Table 1 (continued)

Sex	Age	Gestation	Perinatal Period	Pregnancy	Epilepsy onset(y)	Etiology group	MRI(Normal = 0)	3D MRI	Lesion(hemisph)	Lesion(lobe)	ESES Hemisph	CSWS Index	Global Score
M	8	FT	normal	uneventful	8	Continuous partial epilepsy	1				left	0.99	2
M	6	PT(36w)	normal	uneventful	4	Thalamic + Stroke	1				right	0.94	4
F	9	PT(28w)	Ventr Hemorrhage	uneventful	ns	PVL	1	y	bilateral	multifocal	right	0.69	4
M	14	FT	normal	uneventful	8	SeEAS	0	y	bilateral	multiple	bilateral	0.59	3
M	5	PT(29w)	normal	uneventful	ns	PVL	1				left	0.90	4
F	9	FT	normal	uneventful	8	COVE	0	y	bilateral	multiple	right	0.75	2
M	6	FT	normal	uneventful	3	COVE	0				left	0.61	2
F	4	FT	normal	uneventful	3	LKS	0	y			bilateral	0.94	1
F	4	FT	normal	uneventful	4	SeLECTS	0	y			left	0.84	3
F	8	FT	normal	uneventful	4	SeEAS	0				bilateral	0.82	2
F	4	FT	normal	uneventful	3	SeEAS	0				right	0.55	3

ns: no seizures; PT: pre term; LKS: Landau Kleffner Syndrome; PVL: Peri Ventricular Leukomalacia; MCA: Middle Cerebral Artery.

the test time. A simplified scale was constructed with four domains: Neurological focal signs (including motor and language skills); Behavioral disturbance; Cognitive impairment; School performance regression. Each domain was scored with 1 if present or 0 if absent. A final global score was obtained by the sum of partial domain scores, ranging from 0 (no impairment) to 4 (severe impairment).

3. Results

3.1. CSWS classification

A total of 65 patients were classified as CSWS (Table 1), while the control group included 51 patients (Table A.1). There was no significant difference in the mean age (7.0 ± 2.6 SD years CSWS, 7.2 ± 3.2 SD years Control) (t-test, $p < 0.420$) or gender distribution (Chi-square, $p < 0.796$), between the two groups.

The analysis of the AUC for diverse metrics extracted from the SWI time course and the neurocognitive score (Fig. 1d), demonstrated that the CSWS Index is the best classifier (AUC = 0.92). Despite its good performance, its use in isolation is not enough to completely discriminate CSWS from control patients, as it remains a range of overlap from values around 50% to 70%, (Fig. 1b). Discriminating by the neurocognitive Global Score (Fig. 1e), it becomes clear that while the 50% value for the CSWS Index is effective in the classification of the more disturbed patients (scores 3 and 4), a higher value of up to 70% must be adopted for the less affected ones (scores 0,1, and 2).

3.2. Etiologies

A comparison of the diverse etiologies in the two groups of patients demonstrates important asymmetries, (Fig. 1c): (a) The most frequent causes of symptomatic epilepsies in the control group (cortical dysplasias, dysembryoplastic neuroepithelial tumors (DNET) and tuberous sclerosis) are not represented in CSWS; (b) Thalamic lesions are present in 37% of patients with CSWS (24/65), but only in 8% of the control group (4/51); (c) The focal self-limited epilepsies of childhood are clearly dominant in CSWS, resulting in normal MRIs in most patients, (Fig. 2b). The previous observations suggest that the underlying causes of refractory epilepsies of childhood commonly referred to surgery of epilepsy are distinct from the ones of CSWS, and the latter present a different pattern of subcortical lesions, (Fig. 2a, Table 1).

3.3. Thalamic lesions

The large majority of patients with CSWS and brain structural lesions detected in the MRI ($N = 25$) are associated with thalamic lesions ($N = 24$), representing 43% of the overall CSWS group with MRI results available, which compares with only 10% (4/40) for the control group. Such lesions can be classified into one of five types: (a) Lesions restricted to the thalamus of one hemisphere ($N = 11$); (b) Thalamic lesions associated with more extensive destructive lesions ($N = 3$); (c) Hypothalamic hamartomas ($N = 4$); (d) PVL ($N = 4$); (e) Thalamic hypoplasia associated with polymicrogyria ($N = 1$), (Fig. 2a). Examples of such pathologies can be found in the control group, but with much lower prevalence, (Fig. 2c).

Most patients with lesions restricted to the thalamus had a neonatal acute hemorrhage event (7/11), while for the remaining 4 it was an MRI finding in the context of the CSWS investigation, (Table 1). More extensive lesions were associated with ischemic strokes, mainly of the MCA, in the perinatal period. Peri-Ventricular Leukomalacia was associated with very preterm birth

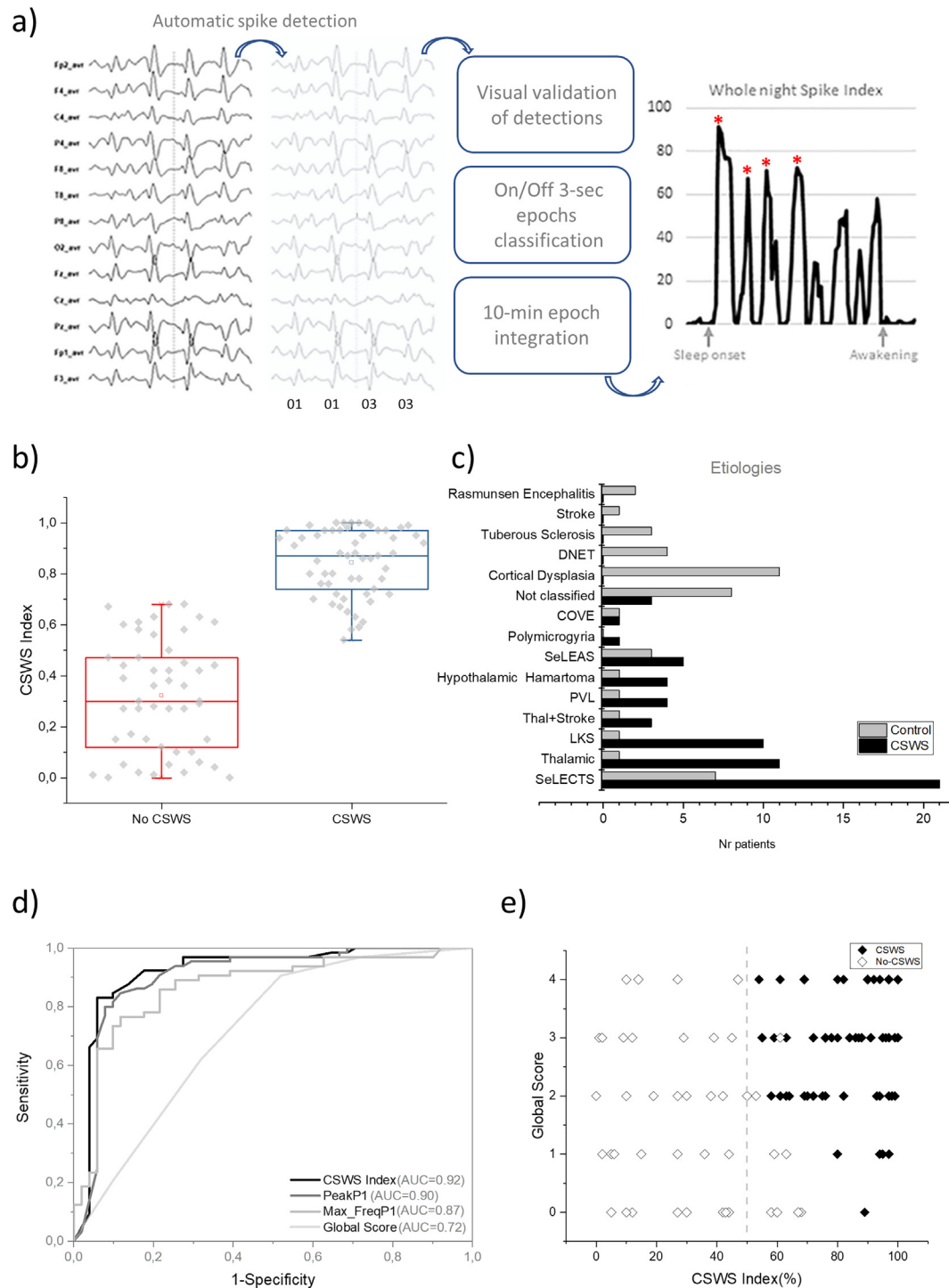


Fig. 1. (a) Schematic representation of processing steps from raw EEG traces (left) to whole-night Spike-Wave Index (SWI, right). The average peak value of the first four sleep cycles (asterisks) was taken as the main metric for classification (CSWS index). (b) Distribution of CSWS Index metric for the CSWS and control groups. (c) Distribution of etiologies between CSWS and control groups. (d) Receiver Operating Curves (ROC) for individual neurophysiological metrics extracted from the SWI time course and the neurocognitive score. The CSWS Index shows a higher AUC and is the best classifier. (e) Scatter plot of CSWS and non-CSWS patients' CSWS Index versus neurocognitive Global Score. For patients with higher scores, an Index of 50% separates well the two groups (dashed line), but a higher value of up to 70% must be used for the lower scores.

in 4/4 patients, while HH presented mostly in full-term births (3/4), with a single case of late preterm, (Table 1).

Thalamic lesions are bilateral in most PVL cases but lateralized in all other types, (Table 1). A reduction of volume is present in comparison with the unaffected thalamus, while the latter demonstrates overall volumes comparable with the ones of CSWS patients

with no structural lesion, (Fig. 2d). The HHs are unique in not reducing thalamic volumes.

A perfect match was found between the hemisphere with the dominant ESES spike pattern and the lateralized thalamic lesion, (Table A.2). For PVL patients with bilateral lesions, ESES hemisphere lateralization is not present in 2 of the 4 patients.

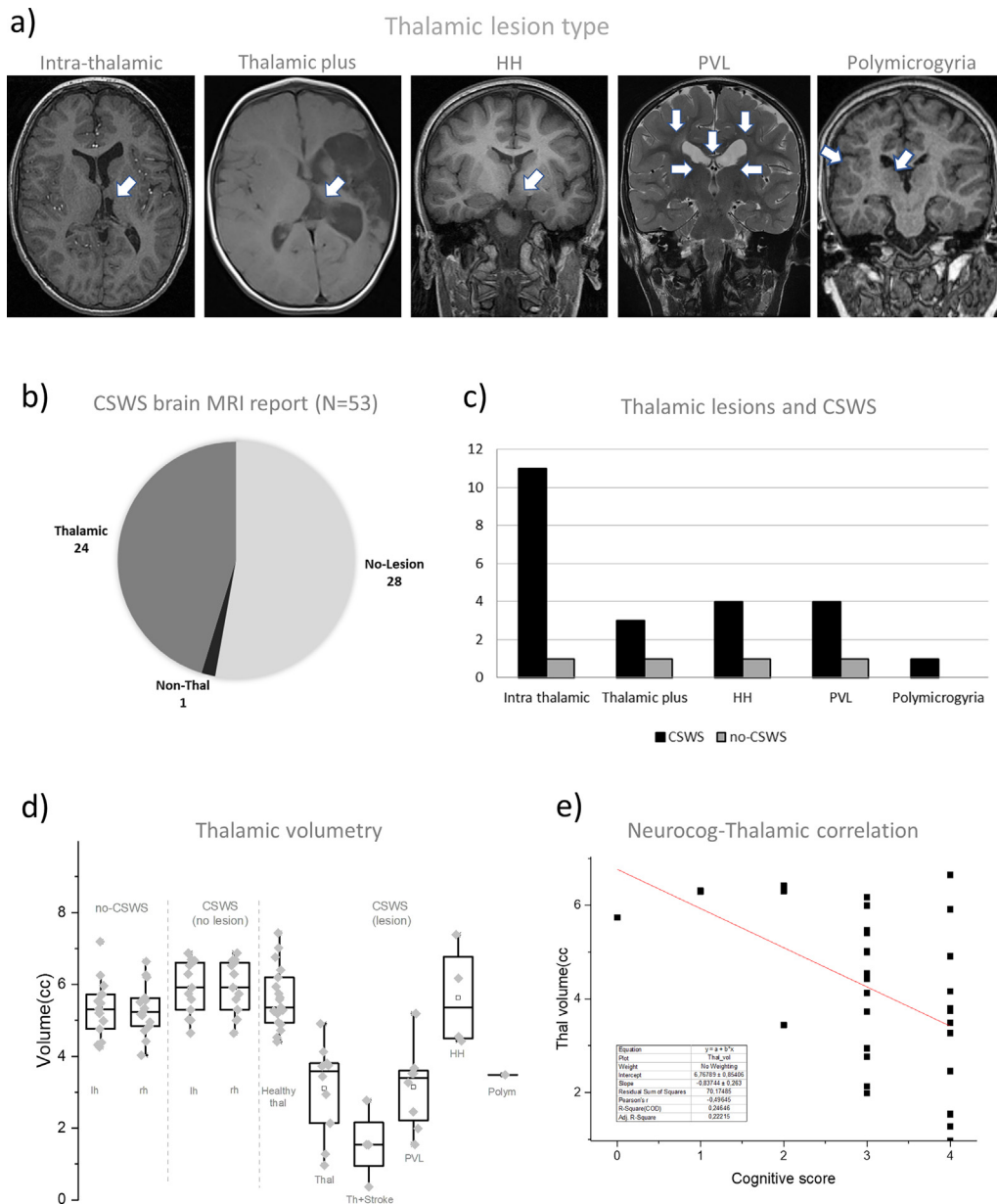


Fig. 2. (a) Main types of thalamic structural lesions found in CSWS patients. These types correlate with hemorrhagic (Intra thalamic), ischemic (thalamic plus, PVL), and dysplastic (HH, Polymicrogyria) etiologies. (b) Brain MRI structural lesions in the 53 CSWS patients with imaging available. Most patients have normal MRIs, while thalamic lesions are present in most patients with abnormal MRIs. (c) Distribution of thalamic lesions in CSWS and control groups, demonstrating the higher incidence in CSWS for all types. (d) Thalamic volumetry (cc) for CSWS patients with and without lesions and control groups. Most thalamic lesions were unilateral, demonstrating volume reduction in comparison with the unaffected ("Healthy thal"), which presented with volumes undistinguishable from control patients and CSWS patients with no lesion. HH patients had normal thalamic volumes, while bilateral involvement was the most common pattern in PVL. (e) The negative correlation between the thalamic volume with the lesion and the neuro-cognitive score suggests a higher dysfunction in patients with the largest destruction.

Visual inspection of lesions in the CSWS group reveals that destructive lesions affected mostly the periventricular thalamic nuclei, the Pulvinar (PULV), and Medio-Dorsal (MD).

3.4. Neurocognitive dysfunction

The global scores from the neurocognitive assessment demonstrate higher scores for CSWS in comparison with the one of the control group, (Fig. 3a), reaching statistical significance in an independence test (Chi-squared test, $p < 0.001$). The comparison between CSWS patients without and with structural lesions, supports higher scores for the latter, with a peak in score 4, while

lesion-free patients peak at score 3, (Fig. 3b), with a significant independence test (chi-squared, $p < 0.002$).

These results put in evidence the more significant neurocognitive dysfunction associated with CSWS with respect to other types of refractory epilepsies of childhood and a more severe impairment when the syndrome is associated with a structural lesion.

4. Discussion

In this study, we demonstrate that early thalamic lesions far from being rare conditions in CSWS are present in most patients with a structural brain injury. Such observation highlights the role of the thalamus in the pathogenesis of the syndrome and estab-

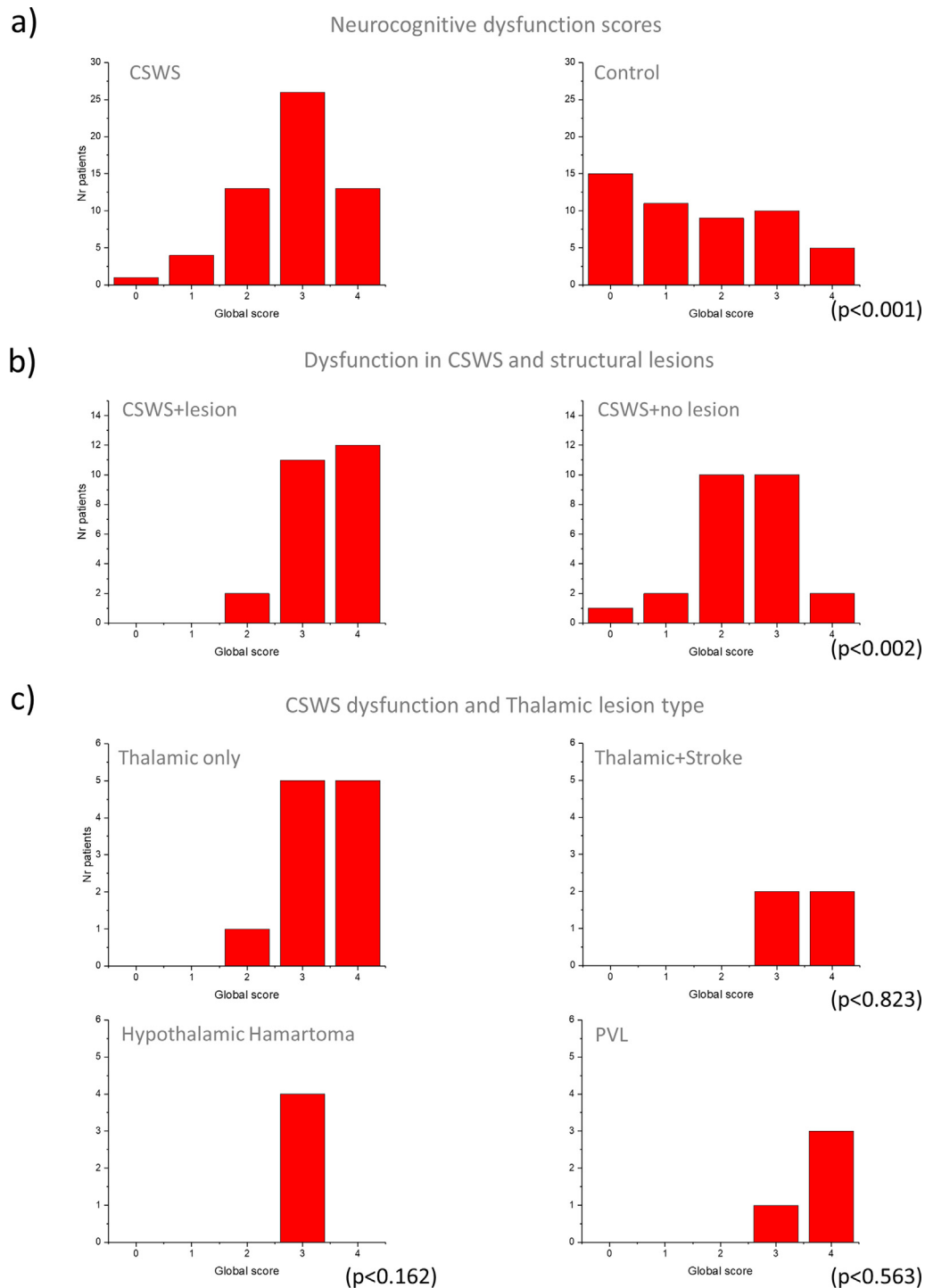


Fig. 3. (a) The cognitive score distributions in CSWS (left) and control (right) patients supports higher scores for CSWS. An independence test (Chi-squared) reached statistical significance ($p < 0.05$). (b) The distribution of cognitive scores in CSWS patients with and without structural thalamic lesions also reached statistical significance in the independence test, with higher scores for patients with the lesion. (c) The distribution of scores for CSWS with diverse types of thalamic lesions did not reach statistical significance in the independence test.

lishes it as the most consistent anatomical correlate of the condition.

In patients with CSWS and structural lesions, the thalamus is affected in most cases and demonstrates a hemispheric lateralization matching the one of ESES and leading to a hemispheric dysfunction. This pattern spans several etiologies previously associated with the syndrome, such as perinatal thalamic hemorrhages, perinatal stroke, HH, PVL, and thalamic hypoplasia

associated with polymicrogyria, and suggests that early thalamic lesions are a common underlying condition leading to CSWS, independently of the associated clinical syndromes.

4.1. Improvement of spike quantification

The methodology for quantification of the SWI has evolved steadily in the last years with the analysis of whole-night EEG

recordings [16], the use of template-based automatic spike detection [13], and the introduction of simplified wearable technology [14]. In this work, we further improve it by introducing a more robust and automated spike detection and defining thresholds for the neurophysiological classification using a data-driven approach. Automated spike detection has been essential for accurate quantification and is traditionally based on template match methods, which not only require a subjective manual visual selection of the appropriate spikes but also can have problems detecting low amplitude spikes and the ones occurring in clusters. Using spike sorting software we largely automated the creation of templates and were able to obtain a more robust detection of spikes throughout the record, resulting in a more accurate determination of the time course of the SWI. The selection of four channels of EEG for template creation could appear as a limiting factor for detecting the sometimes-complex spike topographies. In our experience, this did not prove to be a handicap as the combination of these channels allowed the creation of many separable templates reliably tagging the relevant spike types. The visual inspection of random epochs of the EEG with tags for the diverse spike templates allowed a fast selection of the ones associated with true spikes and elimination of those associated with artifacts, producing a more consistent spike detection than was previously obtained with template matching detection based on spike examples previously selected by the user. While for most patients the spikes showed the well-known tendency to widespread diffusion in sleep, in some they remained strictly focal as was prominently the case for the SeLECTS cases. No patient with primarily generalized epilepsy could be found in our cohort.

The classification of CSWS has traditionally been based on metrics extracted from the SWI time course throughout the night record reaching values higher than a given threshold. The recommended values for these have been postulated by different groups (reviewed in [17]) without a consistent and quantitative estimation based on recorded data, with the ILAE proposing a value of 50% in its classification. In this study, we selected a metric previously published [14] and determined its good classification power using the AUC in ROC curves (Fig. 1e), in patients of our series as compared with control ones. The incorporation of multiple metrics in the classification model could be a strategy to improve the CSWS Index performance and allow better identification of individual cases, in particular the ones with values in the undetermined range of 50–70% (Fig. 1b). In line with this, the addition of the Global Score measuring the neurocognitive impact was effective in improving the separation of CSWS from non-CSWS patients (Fig. 1e), allowing a better classification of individual patients for which the two metrics have been obtained.

4.2. Comparison of the present CSWS series with similar ones from the literature

The 39% of structural brain MRI injuries in our CSWS series compares with the 34% reported by [4], the 49% reported by [18], the 41% reported by [6], the 43% of [3], and the 43% of [5] and supports the previous evidence that most patients have normal MRIs. The percent dominance of the focal self-limited epilepsies of childhood in the MRI-negative cases is also similar in our and other series, covering the full range of these syndromes, as well as the high incidence of CSWS in LKS cases [19]. Nine percent of our patients with CSWS had no history of seizures, which compares with the 22% of Fernandez et al [4], 8% of Maltoni et al [3] and 10% of Sonneck et al [5], while most of the remaining ones exhibited mild epilepsy, with rare cases presenting with frequent seizures. The discrepancy between the mild presentation of seizures and the significant neurocognitive disturbances was a major factor leading the pediatric neurologists to perform a detailed study of CSWS

neurophysiological criteria instead of referring to presurgical assessment. Our results (Fig. 3a) demonstrate that these patients have indeed more severe neurocognitive dysfunction than the control group of mainly surgery for epilepsy cases.

The CSWS series in the present study was based on successive cases referred for neurophysiological assessment in our lab and even though it was not planned to sample the true incidence of the diverse etiologies of CSWS in the population, the finding of a relatively high incidence of thalamic lesions (36%) compared with the incidence of such lesions in other types of epilepsy (for instance 43 out of 5500 in [20]) it is a major finding. It is also higher than the 23% incidence reported by [4] for thalamic and PVL injuries in their series of 100 patients and the 26% found by [5] in 95 patients. This observation reinforces the dominant role of thalamic lesions as the most important single structural abnormality in CSWS.

The relative incidence of the different types of thalamic injury is probably biased as the rare etiologies such as the TH are overrepresented while patients with the more common ischemic strokes are likely underrepresented. This is a common problem found in most published series, leading to significant problems in their comparison and in establishing the true incidence of a number of characteristics of interest. We minimized this limitation by employing strict neurophysiological criteria for patient selection, including whole-night EEG recordings, improved semi-automatic spike detection, and the use of data-driven thresholds for classification. Also, because the main clinical factors leading to the suspicion of CSWS were neurocognitive deterioration and the results of sleep EEGs, with structural lesions playing little if any role, we think that this selection bias does not fully explain the previous findings.

In the construction of the control group, some of the patients were reclassified as CSWS cases after spike quantification and neurocognitive assessment. Notable examples are 4 patients with HH, a condition where cognitive regression is often found and has been attributed to a high seizure burden [21], which met neurophysiological criteria for CSWS. Also, two patients with sequela of perinatal MCA stroke and thalamic lesion previously submitted to surgery for epilepsy were found to meet CSWS criteria not previously recognized. Even though the cognitive regression seen in those patients has been attributed to frequent seizures, the fact that they met CSWS criteria suggests that a contribution of this syndrome is present and could have benefited from proper pharmacological treatment.

4.3. Comparison of CSWS and control groups in etiologies

The different etiologies of the CSWS and control groups (Fig. 1c) clearly suggest that the former patients are not simply a group of severe epilepsies, but a distinct entity, with its own set of associated conditions. The high incidence of thalamic lesions, well beyond the one in the control group of patients, supports an important role of this structural change in CSWS, which spans a range of different etiologies, including hemorrhagic, ischemic, and dysplastic ones, (Fig. 2a).

The periventricular thalamic structural lesions in the perinatal period cross diverse etiologies and suggest that the anatomical injury is a more important factor leading to CSWS years later than the particular pathological processes that originate it. Most of these lesions are destructive and of vascular origin (TH, TH + Stroke, PVL), involving mainly the higher order thalamic nuclei in the periventricular region and leading to an important cortico-cortical intra-hemispheric disconnection, while the more lateral first order nuclei establishing subcortical-cortical connections are relatively preserved. A similar preferential CSWS incidence in medial thalamic nuclei lesions has been described by

[22] in a large series of patients with early thalamic injuries and by [23] in PVL patients. Thalamic injuries in other types of chronic epilepsies were also more frequent in medial nuclei, [20].

HH patients had severe neuro-cognitive impairment (Fig. 3c), in line with similar cases from the literature [21], and presented with epilepsy onset in the first years of life, (Table 1), but did not show thalamic volumetric changes, (Fig. 2d). The fact that they met neurophysiological criteria for CSWS suggests that the mechanism of thalamic dysfunction might be produced by the abundant intrinsic epileptic activity of these lesions instead of fiber destruction.

Our case with perisylvian polymicrogyria and CSWS showed the same lateralized thalamic volume reduction as reported by [24] in the syndrome of polymicrogyria, thalamic hypoplasia, and epilepsy with CSWS.

4.4. Neurocognitive comparison of patients with thalamic lesions and normal MRIs

The more important neurocognitive impairment of CSWS patients with respect to the control group, (Fig. 3a), supports a higher negative impact of CSWS as compared with common refractory epilepsy cases. The additional distinction between CSWS patients with and without lesions, (Fig. 3b), further suggests a range of severity of the underlying dysfunction, from a baseline in patients with common refractory epilepsies to a peak in CSWS with lesions, and CSWS cases with no lesion in an intermediate position.

Liukkonen et al [27] in a group of 32 CSWS patients, 15 idiopathic (atypical SeLECTS and LKS) and 17 symptomatic (mainly perinatal vascular lesions, including 8 thalamic), found as the most common presentation on the neurocognitive domain regression of motor skill (20/32) and language (16/32), behavioral disturbance (13/32) and cognitive deterioration (10/32). These symptoms, like the ones we found in our series, make a significant impact on daily living, are required for the syndrome diagnosis and can be recognized easily in a clinical interview with no requirement for formal assessment. A higher incidence of such presenting symptoms was also reported in the symptomatic group as compared with the idiopathic one, which agrees with our finding of a higher neurocognitive score for CSWS patients with lesions, (Fig. 3b).

4.5. Incidence of cortico-thalamic disconnection in CSWS

Overall, the observation of a high incidence of early thalamic injury in CSWS patients supports the interpretation that thalamic injuries have a much higher incidence than the one obtained from the study of rare perinatal hemorrhages [8,9]. The recognition that the thalamus is involved in most CSWS patients with abnormal MRIs in the present study suggests a much wider scope for thalamic dysfunction in CSWS than it is currently accepted. This is supported by the FDG-PET study of [25] where pathological thalamic abnormalities were found in 18 out of 21 (78%) CSWS patients, mostly with no injuries in the brain MRI. In an EEG-fMRI study of 12 CSWS patients, [26] found spike-related BOLD activation of the thalamus in 5 (41%), 2 with PVL, and 3 with normal MRIs, providing support for an important thalamic involvement in the epileptic network.

Our previous demonstration of a high concordance of the lateralized thalamic lesions with the brain hemisphere exhibiting ESES [10], confirmed in the larger sample of the present study, provides interesting clues for research in patients with normal anatomy. The analysis of the thalamic physiology on the ESES hemisphere of such patients, in comparison with the contralateral thalamus, might provide important insights, that could explain the high incidence of abnormalities in the functional studies [25] of such patients, and also in the recent demonstration of thalamocortical connectiv-

ity abnormalities in SeLECTS [28], its most important etiology, and eventually paving the way for a common mechanism in the CSWS.

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Authors contributions

1. Daniel Carvalho was responsible for most EEG data acquisition and processing and collaborated in writing the paper.

2. Carla Mendonça, Ana Martins, and João Carvalho, Pediatric Neurologists, contributed clinical data for most patients of the study.

3. Alberto Leal was responsible for the conceptual design of the study, data analysis, and writing the paper.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2022.109031>.

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