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Encephalopathy with status epilepticus during sleep: Unusual EEG patterns

Roberto Horacio Caraballo *, Sebastian Fortini, Santiago Flesler, María Constanza Pasteris, Luciana Caramuta, Ernesto Portuondo

Department of Neurology, Hospital de Pediatría "Prof. Dr. Juan P. Garrahan", Buenos Aires, Argentina

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ABSTRACT

Purpose: To retrospectively analyze the electroclinical characteristics, etiology, treatment, and prognosis of patients with epileptic encephalopathy with status epilepticus during sleep (ESES) with unusual EEG features and to corroborate if this series of patients is part of the ESES syndrome.
Method: Charts of 17 patients with typical clinical manifestations of the ESES syndrome with focal ESES of non-REM sleep at onset and during the focal ESES phase, or bilateral synchronic and asynchronic ESES with a symmetric or asymmetric morphology, continuous or subcontinuous and sometimes multifocal paroxysms with or without slow-wave activity during slow sleep seen between 2000 and 2012 were analyzed.
Results: Mean patient follow-up from onset was 7.5 years. An idiopathic cause was found in seven patients, a structural cause in eight, and etiology was unknown in the remaining two. The median age at onset of the unusual ESES syndrome was 7 years. During the ESES phase, 15 children developed new seizure types, negative myoclonus was observed in seven patients, positive myoclonus in five, and absences in nine. Six patients had motor impairment, two had auditory verbal agnosia, and two had motor speech impairment. Attention deficit hyperactivity disorder was observed in four, aggressiveness in six, memory deficit in two, and impaired temporospatial orientation in four.

The patients with focal ESES in the frontal region showed behavioral disturbances and/or motor deterioration, and in those with temporo-occipital involvement the dominant clinical manifestations were language and/or behavioral disturbances.
Conclusion: Our patients with typical clinical manifestations of ESES syndrome but with unusual EEG patterns may be variants of this syndrome.

1. Introduction

Electrical status epilepticus during sleep was first reported in six children by Patry, Lyagoubi, and Tassinari in 1971.[1] Subsequently, Tassinari and colleagues introduced the term encephalopathy related to electrical status epilepticus during sleep (ESES) for the phenomenon.[2,3] The term continuous spikes and waves during slow sleep (CSWSS) was used as a synonym.[2] Recently, the eponym Tassinari syndrome has been proposed for this epileptic encephalopathy.[4,5] Until the terminology is further defined, here we will use the terms epileptic encephalopathy with ESES or ESES syndrome and ESES alone when referring to the EEG manifestations.

The clinical spectrum of and guidelines for the encephalography (EEG) of the ESES syndrome have recently been published.[6–8] The syndrome may be diagnosed when ESES occurs in more than 85% of non-REM sleep; however, authors have used different cut-off rates[4–8] and the classification of the ILAE does not specify the cut-off value.[9] Several authors have described isolated cases with hemi-ESES based on the distribution of epileptiform activity during sleep[10–15] and a series of patients with hemi-ESES has recently been published.[16] Patterns of focal, bilateral asynchronic, and bilateral asymmetric ESES, slow-wave activity, and multifocal spikes or spikes and waves have also been considered,[3,7] but well-described cases with these EEG features during slow sleep have not been published yet.

From the clinical point of view, deterioration of one or more cognitive functions with or without motor, behavioral, and/or

* Corresponding author at: Department of Neurology, Pediatric Hospital Juan P Garrahan, Combate de los Pozos 1881, Buenos Aires CP 1245, Argentina.
Tel.: +54 11 4824 0299; fax: +54 11 4843 6116.
E-mail address: rhcaraballo@arnet.com.ar (R.H. Caraballo).

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psychomotor decline has been described in children associated with ESES.[17,18] Seen from a broader perspective, ESES may be responsible not only for acquired aphasia, but also, and often concomitantly, for other dysfunctions, such as severe behavioral disturbances, apraxia, and negative myoclonus.[2–4] Idiopathic cases and patients with benign childhood epilepsies associated with ESES syndrome have been reported.[19–21] The syndrome may occur in children with structural brain lesions, such as unilateral polymicrogyria (PMG), hydrocephalus, and thalamic lesions.[21–26]

Treatment of the ESES syndrome has frequently been disappointing, but different antiepileptic drug schemes have been proposed.[19,21,23,27–30] In refractory cases, therapeutic alternatives such as corticosteroids, gamma-globulins, the ketogenic diet, and surgery have been tried.[31,32]

The aim of this study was to describe the electroclinical characteristics, etiology, treatment, and prognosis of 17 patients with the typical clinical features of epileptic encephalopathy with ESES but with unusual EEG patterns and to evaluate if these cases are part of the ESES syndrome.

2. Methods

We conducted a retrospective, descriptive study of 17 consecutive patients with clinical features of the ESES syndrome but different EEG patterns seen between 2005 and 2012. All of them met the following inclusion criteria: (1) Onset with focal or apparently generalized seizures and focal EEG discharges; (2) Further appearance of atypical absences and myoclonic, atonic (with or without epileptic falls), and/or generalized seizures; (3) Cognitive impairment and/or behavioral disturbances related to the ESES phase; (4) Focal ESES of non-REM sleep, at onset and during the ESES phase,[2,5] or bilateral synchronic or asynchronic ESES with or without asymmetric morphology, and continuous or subcontinuous, sometimes multifocal paroxysms with or without slow-wave activity during slow sleep. Bilateral synchronic ESES differs from the generalized symmetric pattern in the sense that it is not permanently diffuse and frequently asymmetric. A spike-wave index (SWI) of minimally $\geq$60% was considered. It was evaluated in the maximum SWI during the evolution of ESES.

Focal ESES means the involvement of one or two cerebral lobes. These two patterns included in our study were constant over time. "Continuous" was defined as a permanent EEG abnormality, not interrupted by normal EEG activity, and "subcontinuous" was defined as continuous abnormal EEG activity interrupted by brief periods of normal EEG activity. The EEG abnormalities were analyzed from all charts of our series of patients by the main author.

Patients with an SWI of less 60% associated or not with unusual EEG patterns during sleep but without typical clinical manifestations of ESES syndrome were excluded. Patients with diffuse or hemi-ESES as well as those with other structural epileptic encephalopathies (e.g. myoclonic astatic epilepsy with cognitive deterioration, and Lennox–Gastaut syndrome) and focal epilepsies with secondary bilateral synchronies not fulfilling the criteria for the ESES syndrome were also excluded.

In this study all 17 patients underwent at least four prolonged (more than one hour) sleep EEGs, and nine of them underwent an all-night video-EEG in addition to the routine EEG recordings. The SWI on the non-REM sleep EEG during the ESES phase was visually calculated based on the total number of spikes and waves per unit of time or based on the information provided by the epileptologist in the clinical charts.

Brain magnetic resonance imaging (MRI) was obtained in all patients. Prolonged sleep EEGs were repeated two or more times a year. Data on school achievements and neuropsychological evaluations (Terman-Merrill or WISC III or IV) were repeatedly obtained during the follow-up of 2–9 years. In the absence of formal neuropsychological tests, the degree of cognitive changes was evaluated according to clinical judgment in four patients. The clinical data of the neuropsychological evaluations were obtained when the patients were admitted to the hospital by the same physician.

The onset and the resolution of this unusual ESES phase were defined as the time of onset of cognitive impairment and behavioral abnormalities and the time of significant functional improvement which coincided in all cases with the time of the onset and offset of the pattern on the EEG.

Biochemical controls, urine analysis, and plasma levels of the AEDs were studied. The AEDs and other treatments, such as corticosteroids, the ketogenic diet, and surgery, used before and during the ESES phase were analyzed. Efficacy of the treatment was determined based on electroclinical criteria. Response to treatment of the EEG abnormalities was graded as a normal recording, a more than 75% improvement of the SWI, a more than 50% improvement of the SWI, a more than 30% improvement of the SWI, focalization of the continuous generalized paroxysms, and no response. The percentages of improvement of the SWI were related to the baseline SWI. Clinical response was considered as the decrease of cognitive and behavioral disturbances. The clinical response was graded as complete disappearance of clinical manifestations observed during the unusual ESES phase, and clinical improvement of more than 75%, of more than 50%, or of more than 30%. It was a rough estimation of severity based on the clinical data.

This study was approved by our local ethics committee.

3. Results

3.1. General characteristics

A total of 17 children (10 boys and 7 girls) with an unusual form of the ESES syndrome were identified between March 2000 and April 2012 at the Garrahan Hospital of Buenos Aires.

The probable etiology was idiopathic in seven patients, structural in eight, and unknown in the remaining two. PMG was located in the frontotemporal lobes in three patients and in the parieto-occipital lobes in one. One patient had a bilateral thalamic lesion, one had periventricular leukomalacia, and the remaining structural case had shunted hydrocephalus. From a syndromic point of view, all these patients with structural abnormalities had cerebral palsy, and four also presented with hemiparesis, three with quadriparesis, and one with paraparesis. Mental retardation was mild in two and moderate in six; four of these children had had behavioral disturbances before the onset of the ESES.

Of 17 patients, two had a positive family history and one a positive personal history of febrile seizures.

3.2. Seizures and EEG findings before the onset of the unusual ESES

All children except two had experienced focal motor seizures before the onset of ESES. In four (23.5%) the seizures were associated with loss of consciousness. Seven (41%) had had focal seizures with secondary generalization, and three (17.6%) had had apparently generalized seizures. Atypical absences were found in five patients (29.4%). Tonic seizures were not registered. Ten patients (58.8%) only had had seizures during the sleep, two (12%) only had had seizures while awake, and five (29.4%) had had seizures during sleep and while awake.

The current median age of the patients is 11 years (range, 9–17 years). The median age at onset of focal epilepsy was 3 years (range, 1–8 years). Median time elapsed between the first focal

seizure and the onset of the unusual ESES syndrome was 5 years (range, 2–7 years).

Before the onset of the unusual ESES, the awake EEG recordings showed focal epileptiform abnormalities in 10 patients (58.8%), that were multifocal in three (17.6%) and focal, associated with generalized paroxysms in four patients (23.5%). In this period, the paroxysmal discharges became more frequent on the sleep EEG recordings. Asymmetric baseline EEG activity was found in seven (41%) cases.

In the phase immediately previous to ESES onset, a considerable increase of the interictal focal abnormalities was observed in 11 patients and of the multifocal and generalized abnormalities in the remaining six, predominantly in the anterior regions, both during wakefulness and sleep.

3.3. Clinical features and EEG findings in the unusual ESES syndrome phase

The median age at onset of the unusual ESES syndrome was 7 years (range, 6–10 years). The mean duration of ESES was 13 months (range, 5–30 months).

Fourteen (82.3%) of the 17 patients continued having seizures during ESES period. Ten (58.8%) of them had more severe seizures. Fifteen patients (88.2%) of 17 also presented with new seizure types during the unusual ESES period. These seizures were negative myoclonus in seven patients (41%), positive myoclonus in five (29.4%), and absences in nine (52%). Six patients had motor impairment secondary to negative myoclonus, two had auditory verbal agnosia, and two had motor speech impairment (non-verbal auditory agnosia).

When the children deteriorated, the following cognitive disturbances were observed: Attention deficit hyperactivity disorder in four (23.5%), language deterioration – nonverbal agnosia – in two (11.7%) and verbal auditory agnosia in two patients (11.7%), aggressiveness in six (35.2%), memory deficit in two (11.7%), impaired temporospatial orientation in four (23.5%), and loss of bladder control in two patients (11.7%). Baseline cognitive status was affected in nine patients (52%). The features of the new cognitive involvement were fundamentally different from those of baseline cognitive function before the onset of the unusual ESES period.

During the ESES phase, the awake EEG recording showed more frequent focal abnormalities, multifocal spikes, and bilateral spikes and waves at 2–3 Hz, predominantly in the anterior regions. Additionally to the focal ESES, the sleep EEG recordings occasionally showed focal epileptic activity in the contralateral hemisphere in ten patients (58.8%); two of them also had isolated bilateral epileptic activity. Bilateral synchronic and asynchronic ESES was seen in seven (41%); continuous or subcontinuous activity with asymmetric morphology in three of them, and multifocal spikes and spikes and waves during slow sleep in five of them. Bilateral asynchronic and asymmetric slow waves were also observed in five of these seven patients. Clinical manifestations were similar to classic cases with the ESES syndrome in all seven patients. Six of them had structural lesions and in the remaining one the etiology was unknown. In two patients ESES recurred, twice in both of them.

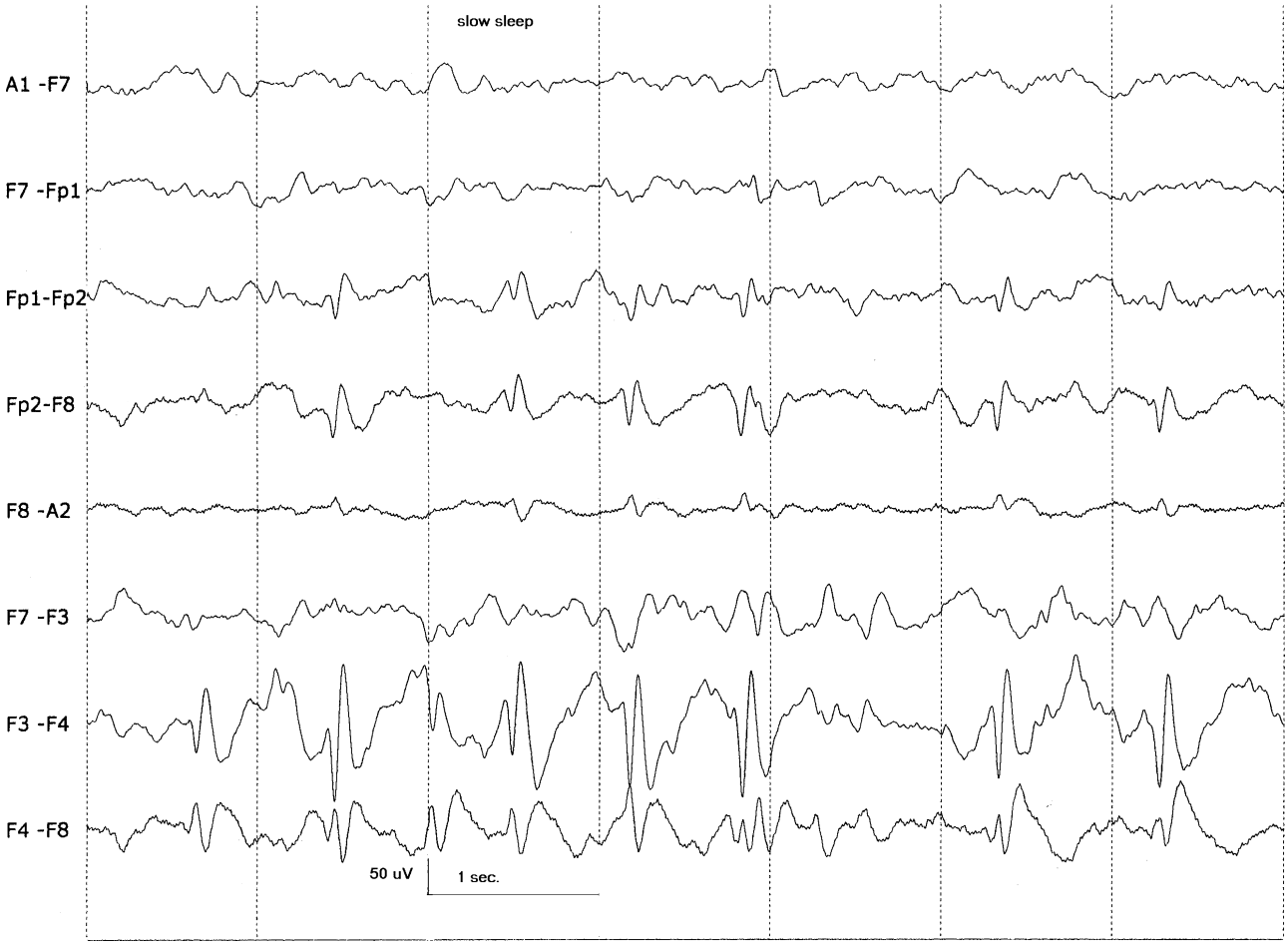

Fig. 1. An 8-year-old boy with motor deterioration. The sleep EEG recording shows continuous spike-and-wave discharges in the right frontal lobe.

In the first group of ten patients with focal ESES, we found three electroclinical subgroups. The first subgroup of five patients was characterized mainly by negative and/or positive myoclonias with motor deterioration and/or behavioral disturbances associated with focal ESES located predominantly in frontal regions (Fig. 1); the second subgroup of two patients was characterized by verbal auditory agnosia associated with focal ESES predominantly in temporal lobe (Fig. 2); and the third subgroup of three cases was characterized by absences, focal seizures with or without generalized tonic-clonic seizures, and behavioral and cognitive disturbances associated with non-verbal agnosia in one of them (Fig. 3). The main EEG pattern was focal temporo-occipital ESES. Seven of these 10 cases were idiopathic.

The second group of seven patients (41%) with typical clinical manifestations of the ESES syndrome had bilateral synchronic and asynchronic ESES with or without asymmetric morphology, continuous or subcontinuous and sometimes multifocal paroxysms with or without slow-wave activity during slow sleep (Fig. 4). Bilateral asynchronic and asymmetric slow waves were also observed in five of these seven patients (Fig. 5). Etiology was structural in six of them and unknown in the remaining one. In two patients ESES recurred, twice in both of them. In this group no well-defined subgroups were identified.

All the patients included in this study had an SWI of ≥85%, except three/10 first-group patients and one/seven of patients in the second group, who had an SWI between 60% and 85%.

In Table 1, general features, seizures, and EEG findings before and throughout the ESES phase according to etiology and SWI are described.

3.4. Treatment

Outcome according to electroclinical criteria was: (a) seizure freedom and repeated sleep EEGs showing disappearance of the focal ESES in four patients, all with an idiopathic etiology; (b) a significant reduction in seizure frequency (more than 75%) and improvement of more than 75% of the SWI in three patients, two with ESES syndrome secondary to PMG and one with an idiopathic cause; (c) a 50–74% seizure reduction, and improvement of more than 50% of the SWI in three patients, two with ESES syndrome secondary to shunted hydrocephalus and a thalamic lesion, respectively, and of unknown etiology in the remaining one; (d) a 30–49% seizure reduction and improvement of more than 30% of the SWI in two, one with ESES syndrome secondary to PMG and one with idiopathic ESES syndrome; and (e) no response in five patients.

Successful epilepsy surgery was performed in one patient. In this patient, considering the refractoriness of the seizures after failure of different adequate high-dose AED schemes over a prolonged period of time added to a bad quality of life, a presurgical evaluation was done. All seizures were shown to arise from the focal lesion secondary to unilateral polymicrogyria. Partial lesionectomy was performed.

In a patient with hemiparetic cerebral palsy secondary to periventricular leukomalacia the focal ESES recurred twice, the first time due to levetiracetam, and the second time with vigabatrin; in both situations withdrawal of these AEDs significantly improved the electroclinical picture. Both AEDs were prescribed prior to referral to our department.

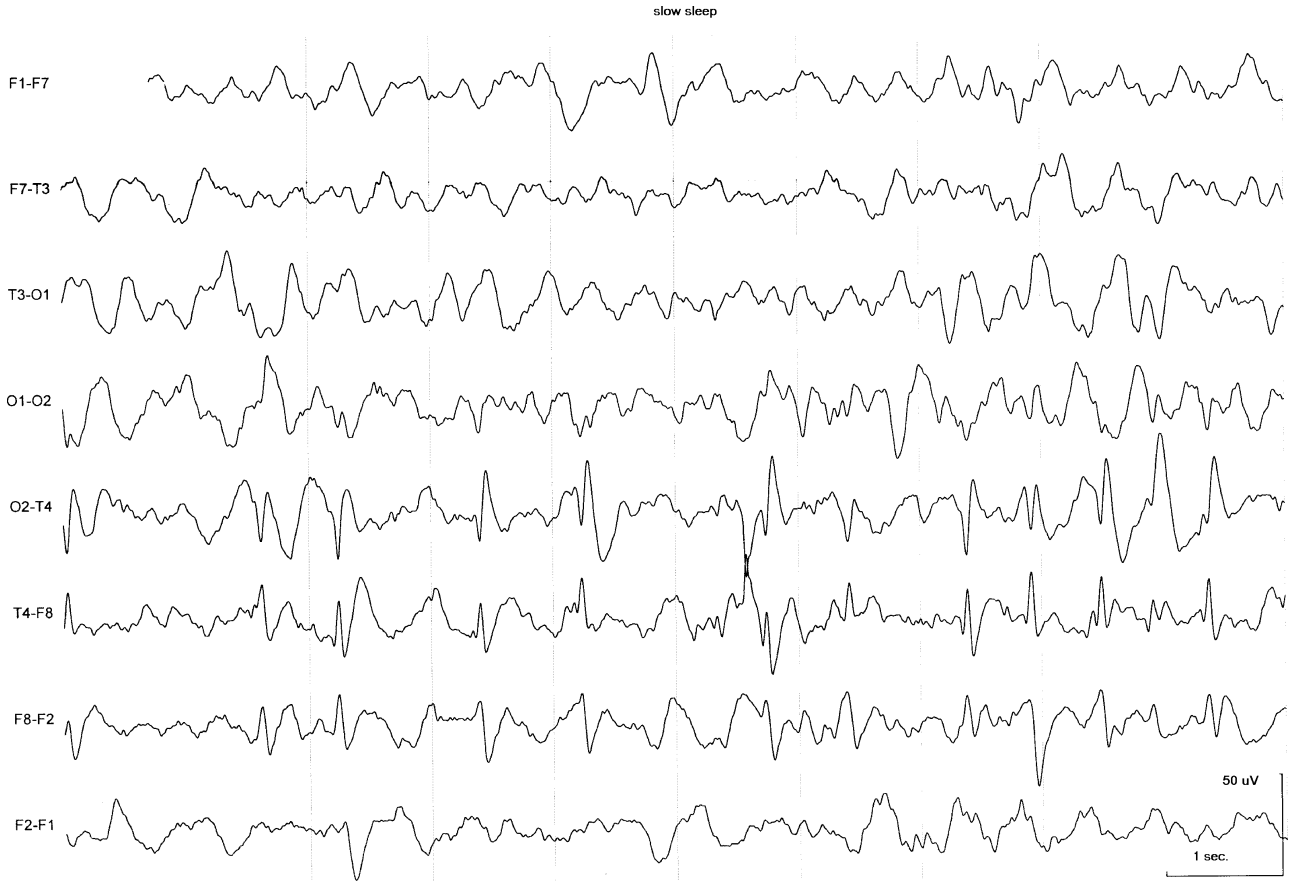

Fig. 2. A 10-year-old girl with verbal auditory agnosia. The interictal sleep EEG recording shows right subcontinuous temporal spikes.

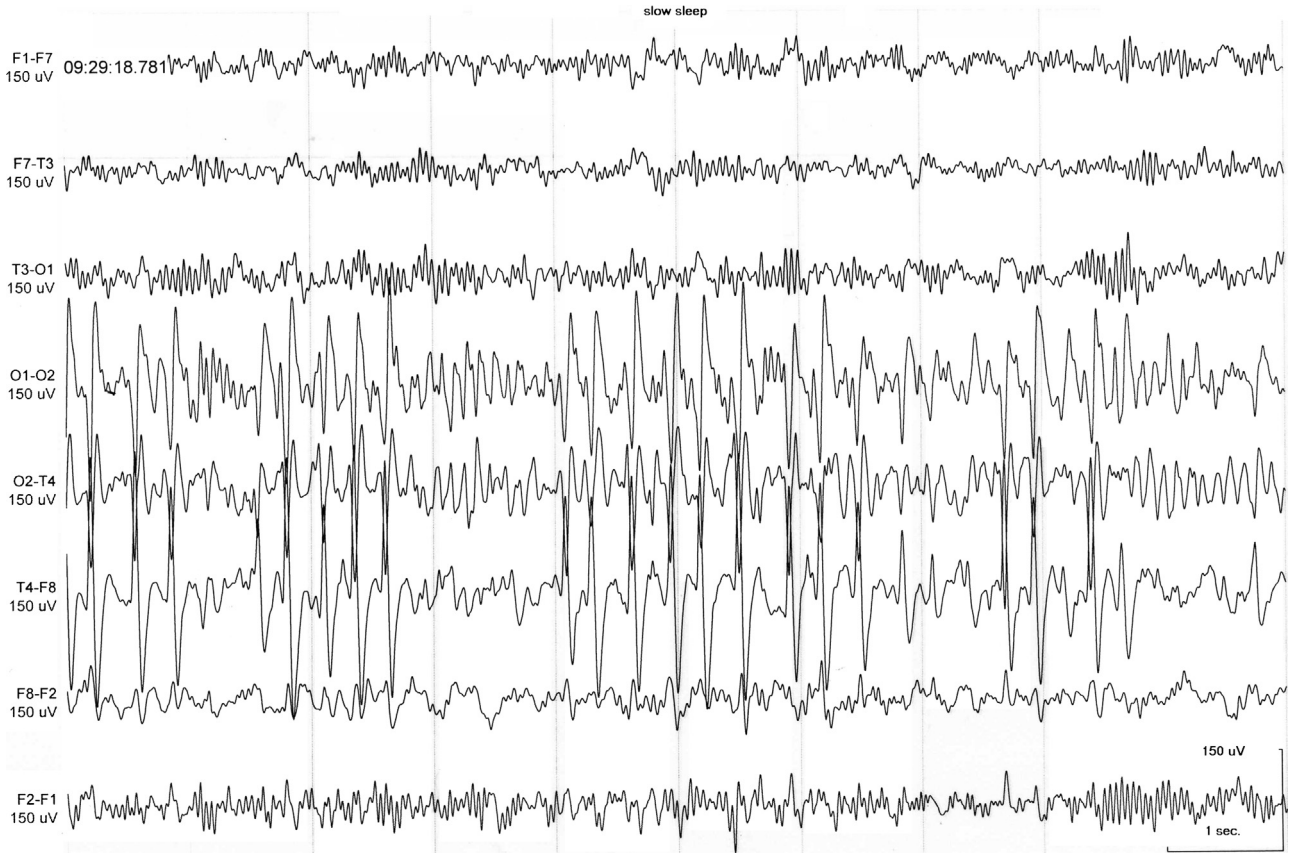

Fig. 3. A 9-year-old boy with severe behavioral disturbances, frequent atypical absences, and focal motor seizures. The sleep EEG recording shows high-frequency spikes in the right temporal region.

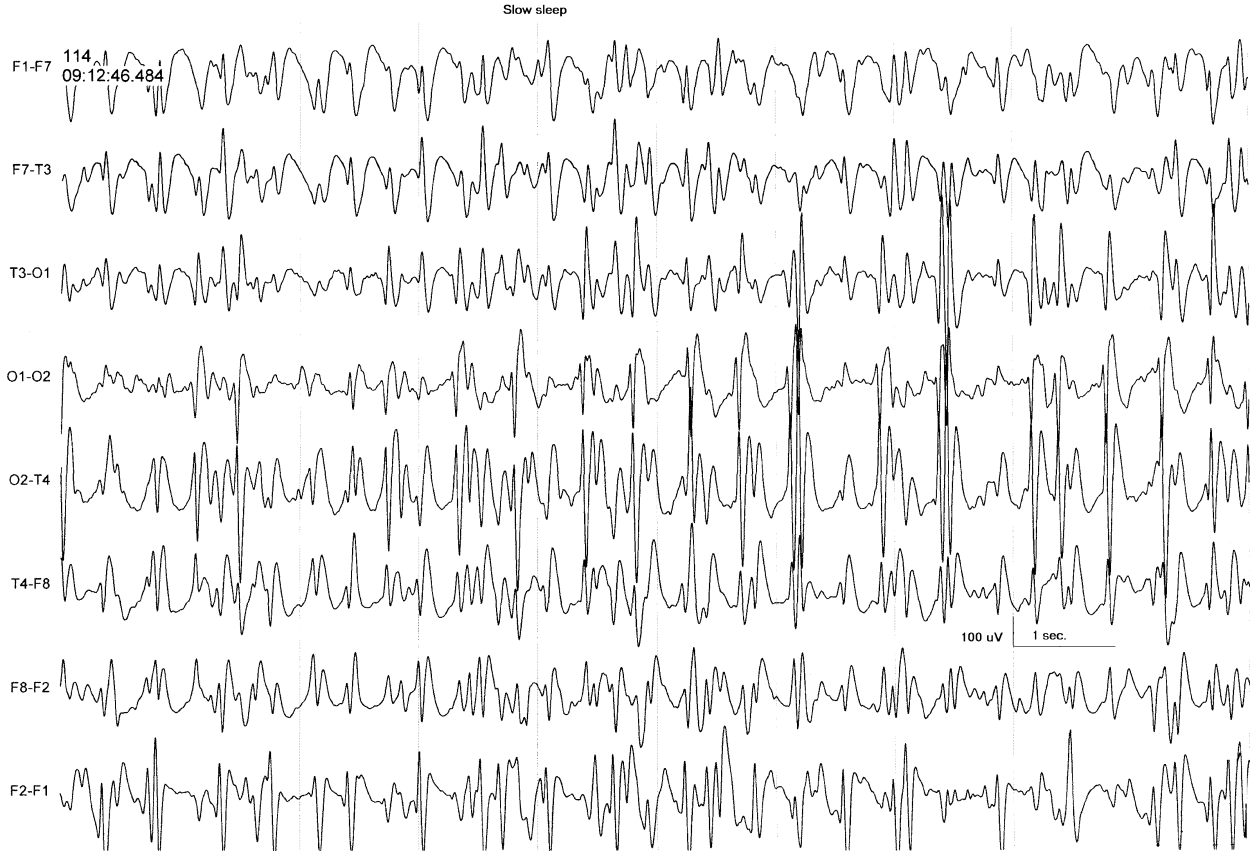

Fig. 4. Sleep EEG recording shows bilateral, continuous synchronic and asynchronic spikes and waves. Asymmetric morphology of the bilateral paroxysms is also observed.

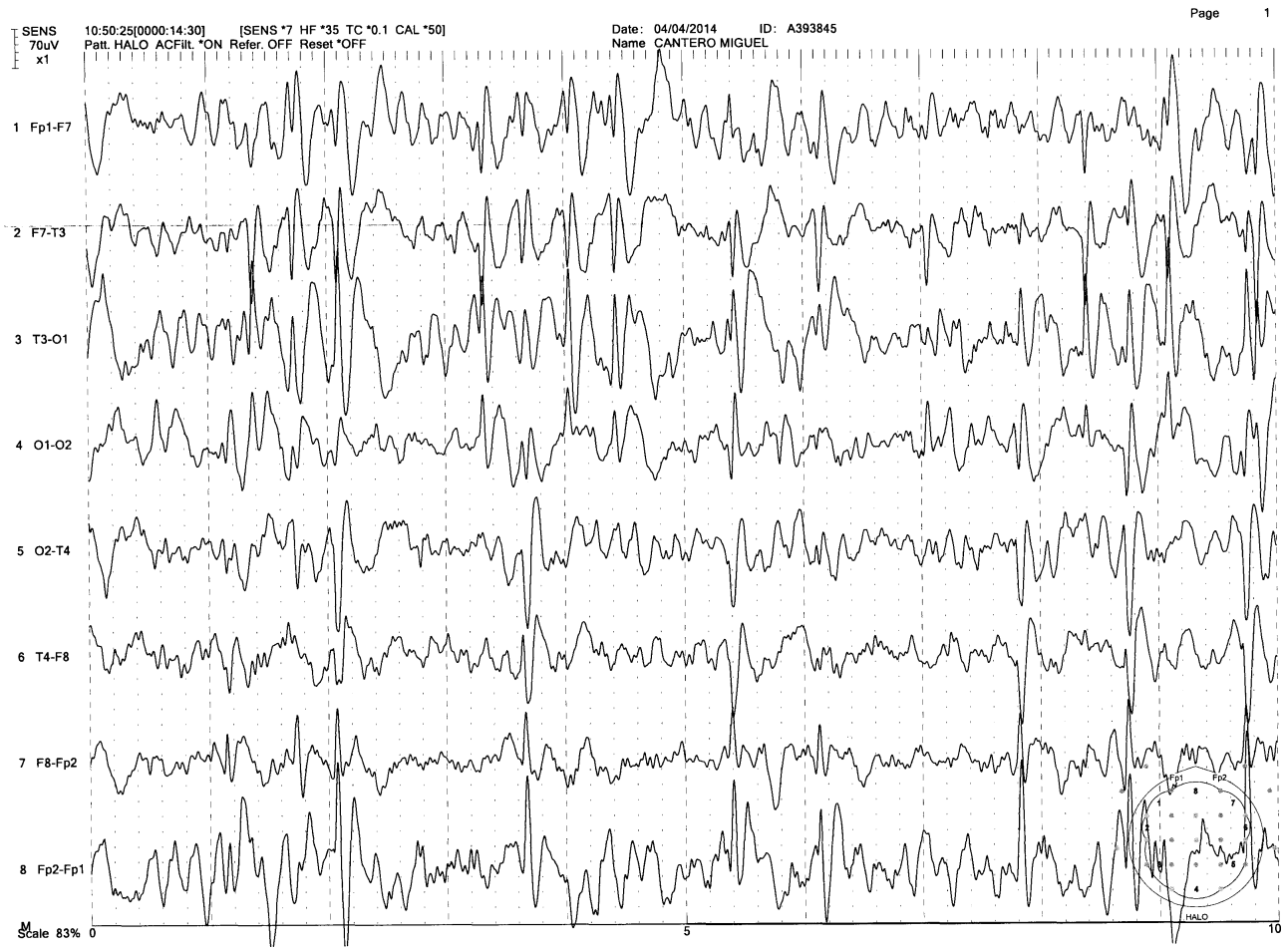

Fig. 5. The same patient as in Fig. 4; the sleep EEG recording also shows multifocal spikes and slow waves.

In Table 2, we describe treatment results of our series of patients during the ESES phase.

3.5. Outcome

Average follow-up after ESES onset was 7.5 years (range, 2–10 years). At the last control, three patients had become seizure free and five patients had sporadic seizures. The EEG showed focal spikes in four, multifocal spikes in three, and bilateral symmetric and asymmetric spikes in six patients. Seizures were yearly in two, half-yearly in two, and bi-monthly or monthly in five. Five patients did not respond well to treatment.

In our study definitive seizure control and normalization of the EEG depended on the etiology of the ESES syndrome. The best results were found in the idiopathic cases and in those with unilateral PMG. ESES disappeared in most of them and the patients with ESES syndrome secondary to PMG have only sporadic seizures. In the post ESES phase the duration of the EEG abnormalities was significantly longer in the patients with underlying brain lesions.

In patients who became seizure free and in those who had a seizure reduction of more than 75%, school performance and IQ have improved significantly and they have returned to baseline cognitive function; however, it should be noted that in some of the children with structural ESES, it is difficult to evaluate the neuropsychological profile during the active period of epilepsy, mainly in the ESES phase.

4. Discussion

By definition, our series of patients had clinical features of epileptic encephalopathy with ESES with focal ESES and bilateral synchronic and asynchronic ESES, with or without asymmetric morphology, and continuous or subcontinuous, sometimes multifocal paroxysms during slow sleep. Our study confirms that these cases have electroclinical features compatible with an epileptic encephalopathy similar to the classic form of the ESES syndrome. It has been stated that the EEG inclusion criteria should be revised or better defined, which additionally will be useful to determine the boundaries between ESES and other syndromes. Thus, certain EEG markers in patients with the ESES syndrome, such as focal ESES, asynchronic bilateral paroxysms with an asymmetric morphology, multifocal paroxysms, and slow waves should be investigated to define the role of these EEG abnormalities in this particular syndrome.

It is interesting to emphasize that there were two groups with typical clinical features of the ESES syndrome: The first associated with focal ESES and the second with bilateral synchronic and asynchronic ESES with or without asymmetric morphology, and continuous or subcontinuous, sometimes multifocal paroxysms with or without slow-wave activity during slow sleep. In the first group three subgroups were recognized: The first subgroup was characterized by negative and/or positive myoclonias associated or not with behavioral disturbances and/or motor deterioration associated with focal frontal ESES; in the second, the main clinical

Table 1
General features, seizures, and EEG findings before and throughout the ESES phase according to etiology and SWI.

General characteristics and electroclinical findings	Focal ESES (frontal)	Focal ESES (temporal)	Focal ESES (temporo-occipital)	Bilateral synchronic and asynchronic ESES, SW (5p) MF (1p)	Bilateral synchronic and asynchronic ESES, and MS
Number of patients	5	2	3	5	2
Neurological examination	Moderate Hemiparesis 1 p	–	Moderate Hemiparesis 1p	Moderate Hemiparesis 1p Quadriparesis 2p Paraparesis 1p	Moderate Hemiparesis 1p Quadriparesis 1p
Mental retardation	Mild 2p	–	Moderate 1p	Moderate 3 Severe 2	Moderate 1p Severe 1p
Type of seizure (pre-ESES period)	MFS, SGTCS	MFS, CFS	MFS, AA	MFS, CFS, SGTCS, AA	MFS, CFS, SGTCS
EEG during sleep and while awake (pre-ESES period)	Focal spikes, and bilateral spikes	Bilateral spikes	Focal spikes, and bilateral spikes	Focal spikes, bilateral spikes, and multifocal spikes	Focal spikes, multifocal spikes
New type of seizure ESES period	Negative myoclonias, and positive myoclonias,	AA 1p	Myoclonias, AA	AA, myoclonias, MFS, SGTCS	AA, myoclonias, MFS
Other EEG findings ESES period	Focal spikes, and bilateral	Bilateral spikes	Focal spikes, and bilateral	SW, and MS	Focal spikes, and MS
Verbal auditory agnosia	–	+	–	–	–
Motor deterioration	+	–	–	+	–
Cognitive dysfunction	–	–	+	+	+
Motor speech impairment	–	–	+	+	+
Behavioral alterations	–	–	+	+	+
Residual deficit	–	Language deficit (1p)	Behavioral and cognitive deficits (2p)	Behavioral and cognitive deficits (3p)	Behavioral and cognitive deficits (1p)

p: patient; MFS: motor focal seizures; CFS: complex focal seizures; SGTCS: secondarily generalized tonic-clonic seizures; AA: atypical absences; MS: multifocal spikes; SW: slow waves.

Table 2
Treatment data of our series of patients during the ESES phase.

Negative response	Positive response	Transient response
- Lamotrigine[a] 3 p	- Clobazam and ethosuximide 2 p	- Levetiracetam 2 p
- Topiramate[a] 4 p	- Clobazam + sulthiame 1 p	- Valproic acid + ethosuximide 2 p
- Phenobarbital[a] 2 p	- Ethosuximide + valproic acid 2 p	- Clobazam + ethosuximide 1 pat
- Carbamazepine[a] 3 p	- Ethosuximide + sulthiame 1 p	- KD 1 p
- Valproic acid[a] 3 p	- Ethosuximide + clobazam + sulthiame 1 p	
- Levetiracetam[a] 2 p	- Corticosteroids + clobazam + valproic acid 2 p	
- Ethosuximide 1 p	- KD + clobazam + sulthiame 1 p	
- Sulthiame 1 p	- Surgery 1 p	

p: patient; KD: ketogenic diet.
[a] Antiepileptic drugs that worsened the electroclinical features of ESES.

manifestation was verbal auditory agnosia associated with focal temporal ESES; and the third subgroup was predominantly characterized by behavioral disturbances, with absences and/or focal seizures with or without generalized seizures associated with focal temporo-occipital ESES. In the second group no subgroups were recognized.

Based on the neuropsychological status acquired during the ESES phase, Rousselle and Revol,[33] identified three groups. The first includes neuropsychologically healthy children, the second cases with verbal auditory agnosia, and the third group children with global neuropsychological and cognitive impairment. The main epileptogenic focus in children with aphasic manifestations was temporal and in those with global neuropsychological deterioration it was frontal. However, it is well known that predominantly frontal spikes may be associated with negative or positive myoclonias.[34] Thus, according to spike location some clinical variation, with behavioral or motor phenomena, may be recognized.[35]

Focal ESES may be the only EEG marker of the epileptic encephalopathy with ESES as in some of the patients presented here. In our experience, focal ESES may be part of the classical ESES syndrome in the initial ESES period evolving into diffuse ESES or a relapse of the ESES phase.

In our second group, the typical clinical manifestations of the ESES syndrome were associated with bilateral synchronic and asynchronic ESES with or without an asymmetric morphology, continuous or subcontinuous, sometimes multifocal paroxysms during slow sleep; all the patients in this group were structural cases.

The characteristics of these patterns should also be taken into account as EEG markers in the development of the encephalopathic epileptic mechanisms. Neurophysiological and functional studies are necessary to define the exact EEG features that should be considered as inclusion criteria of this syndrome. Additionally, in the clinical practice recognition of these unusual EEG patterns associated with neurological deterioration, regardless of the SWI, is fundamental to manage these patients accordingly.

It seems that continuous activation of paroxysmal activity during sleep in a focal cerebral region may cause neuropsychological dysfunction, and this finding appears to be similar to bilateral or diffuse ESES in determining neurological deterioration.[12,18,33–35] Thus, the age-dependent epileptiform discharges in a particular period of sleep per se, regardless of their distribution, synchrony or asynchrony, and morphology, may play a crucial role in the development of cognitive deterioration.[7,8,12,36–38] In some patients of our series with bilateral brain involvement slow waves were also found and therefore it may be interesting to determine the impact of this abnormal EEG activity in this period of sleep in developing deterioration.[22–26]

As may occur in the classic ESES syndrome, markedly abnormal neuronal activity during a critical period for synaptogenesis may result in aberrant synapse formation, explaining this poor neuropsychological outcome.[12] The synaptic homeostasis hypothesis predicts that the strength of synapses is decreased during sleep. The downscaling process during sleep may contribute to the developmental regression in children with ESES.[38]

It is interesting to note that the second of these two unusual ESES patterns we found, characterized by bilateral synchronic and asynchronic activity, with a different morphology of the paroxysms, and sometimes multifocal spikes with slow waves, may occur during a single sleep EEG recording, or different features may appear in different combinations. This raises some important questions, for example: What is more aggressive for the brain function, the quality of the EEG discharges and slow waves, the quantity of the discharges, or both?

Future electroclinical studies are necessary to delineate the exact clinical and EEG features of this intriguing epileptic encephalopathy.

5. Conclusions

Our study demonstrates that unusual ESES patterns have clinical features compatible with an epileptic encephalopathy similar to the classic form of the ESES syndrome.

The patients described in this study confirm the existence of two subgroups, the first with focal ESES associated with clinical manifestations related to the location of the focal epileptogenic region and the second subgroup characterized by bilateral synchronic or asynchronic ESES with or without asymmetric morphology, continuous or subcontinuous, sometimes multifocal paroxysms with or without slow-wave activity.

The prognosis of these patients depends on the etiology rather than on the EEG markers. The idiopathic group had a better outcome.

Patients with cognitive and/or motor deterioration who had a good response to AEDs returned to baseline neurological development, whereas in the drug nonresponders it continued to deteriorate.

Disclosure

All co-authors have read and agreed to the content of the manuscript. None of the authors has any conflict of interest to disclose, nor any financial or commercial involvement and any contribution of industry-sponsored research or of corporate participation in preparing the manuscript. We confirm that we have read the Journal's position on issues involving ethical publication, and affirm that this report is consistent with those guides.

Conflict of interest statement

We disclose no financial and personal relationships with other people or organization that could inappropiately influence this work.

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