Epilepsy & Behavior 97 (2019) 244–252

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Idiopathic encephalopathy related to status epilepticus during slow sleep (ESES) as a "pure" model of epileptic encephalopathy. An electroclinical, genetic, and follow-up study

Elena Pavlidis [a,b,c,*], Rikke S. Møller [a,d], Marina Nikanorova [a,d], Margarethe Sophie Kölmel [a], Pia Stendevad [a], Sandor Beniczky [a,e,h], Carlo Alberto Tassinari [f], Guido Rubboli [a,g,**,1], Elena Gardella [a,d,1]

[a] Danish Epilepsy Centre - Filadelfia, Dianalund, Denmark
[b] Child Neuropsychiatry Unit, Department of Neuroscience, University of Parma, Parma, Italy
[c] Child Neuropsychiatry Service of Carpi, Mental Health Department, AUSL Modena, Carpi, Italy
[d] Department of Regional Health Research, University of Southern Denmark, Odense, Denmark
[e] Department of Clinical Neurophysiology, Aarhus University Hospital, Aarhus, Denmark
[f] University of Bologna, Bologna, Italy
[g] Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[h] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

ARTICLE INFO

Article history:
Received 23 April 2019
Revised 20 May 2019
Accepted 21 May 2019
Available online 26 June 2019

Keywords:
ESES
Epileptic encephalopathy
Status epilepticus
Slow sleep
Sleep homeostasis

ABSTRACT

Objective: The objective of the study was to investigate electroclinical and neuropsychological features, genetic background, and evolution of children with idiopathic encephalopathy with status epilepticus during slow sleep (ESES), including Landau–Kleffner syndrome (LKS).
Material and methods: All children diagnosed with idiopathic ESES at the Danish Epilepsy Centre between March 2003 and December 2014 were retrospectively reviewed. Repeated 24-hour electroencephalography (24-h EEG) recordings, neuropsychological assessments, and clinical–neurological evaluation were performed throughout the follow-up in all patients. In 13 children, genetic investigations were performed.
Results: We collected 24 children (14 males and 10 females). Mean age at ESES diagnosis was 6 years, and mean ESES duration was 2 years and 7 months. Twenty-one children had epileptic seizures. Three children had LKS. Topography of sleep-related EEG epileptic abnormalities was diffuse in 3 subjects, hemispheric in 6, multifocal in 9, and focal in 6. During the active phase of ESES, all children presented with a heterogeneous combination of behavioral and cognitive disturbances. In 14 children, a parallel between severity of the clinical picture and spike–wave index (SWI) was observed. We could not find a strict correlation between the type and severity of neurobehavioral impairment and the side/topography of sleep-related EEG discharges during the active phase of ESES. At the last follow-up, 21 children were in remission from ESES. Complete recovery from neurobehavioral disorders was observed in 5 children. Genetic assessment, performed in 13 children, showed *GRIN2A* variant in two (15.4%).
Significance: Our patients with idiopathic ESES showed a heterogeneous pattern of epileptic seizures, neurobehavioral disorders, and sleep EEG features. Only one-fourth of children completely recovered from the neuropsychological disturbances after ESES remission. Lack of correlation between severity/type of cognitive derangement and SWI and/or topography of sleep EEG epileptic abnormalities may suggest the contribution of additional factors (including impaired sleep homeostasis due to epileptic activity) in the neurobehavioral derangement that characterize ESES.

1. Introduction

Encephalopathy related to status epilepticus during slow sleep (ESES) (otherwise labeled as continuous spikes and waves during sleep (CSWS)) is an age-related epileptic syndrome characterized by deterioration of cognitive functions and behavior, epilepsy with various seizure types, and a characteristic EEG pattern characterized by extreme

* Correspondence to: E. Pavlidis, Child Neuropsychiatry Service of Carpi, Mental Health Department, - AUSL Modena, Piazzale Donatori di Sangue 3, 41012 Carpi, Italy.
** Correspondence to: G. Rubboli, Danish Epilepsy Centre, Filadelfia/University of Copenhagen, Kolonivej 1, 4293 Dianalund, Denmark.
E-mail addresses: e.pavlidis@ausl.mo.it (E. Pavlidis), guru@filadelfia.dk (G. Rubboli).
[1] Senior authors and equal contribution.

https://doi.org/10.1016/j.yebeh.2019.05.030
1525-5050/

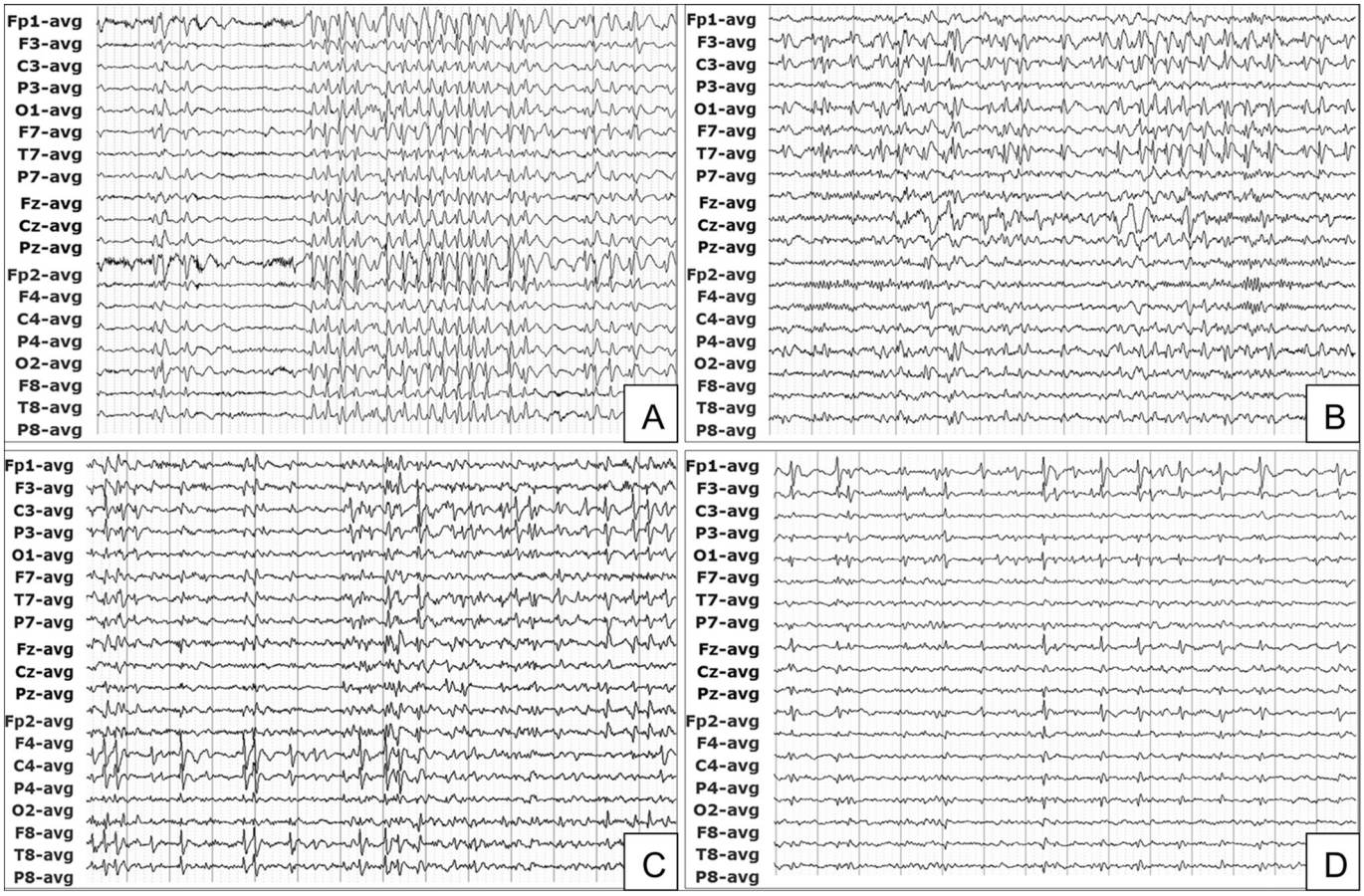

Fig. 1. Different patterns of ESES topography observed during the 24-h EEG recordings. A) Diffuse ESES pattern: bilateral and quite diffuse epileptiform abnormalities; B) hemispheric ESES pattern: localized to one hemisphere without or with negligible spread to the contralateral; C) multifocal: multiple foci either in the same hemisphere or in both hemispheres; D) focal: the epileptic abnormalities were located in one or two lobar regions of the same hemisphere. Notably, the number of patients for each group refers to the time of maximum SWI. Anyway, in the same patient, the ESES pattern could change several times at different controls.

activation of epileptiform discharges during slow sleep, i.e., status epilepticus during sleep (SES) that, in the original description, occupied at least 85% of non-rapid-eye-movement (NREM) sleep [1,2]. Despite the long-term favorable outcome of epilepsy and electrographic SES, the prognosis of this condition is guarded because of the possible persistence of severe neuropsychological and behavioral disturbances into adulthood. Etiology of ESES can be either idiopathic, symptomatic, or unknown. In recent years, variants in *GRIN2A* and *CNKSR2* have been found to be associated with the epilepsy–aphasia spectrum, including ESES [3–7].

Several reports have described the electroclinical features and long-term outcome of cohorts of children with ESES with heterogeneous etiologies (see also Tassinari et al. for a review [2]) [8–14] or pooled together with other conditions [15] whereas idiopathic ESES has been the subject of only one paper focused on the cognitive and behavioral long-term consequences [16].

In our study, we report the electroclinical features, the genetic findings, and the long-term evolution of a homogeneous cohort of patients with idiopathic ESES and normal neurodevelopment before ESES onset. In this respect, our population of children with ESES may illustrate the "pure" effects of the extreme activation of epileptiform discharges during NREM sleep (i.e., SES) in the development of severe cognitive and behavioral impairments and its long term consequences, without other possible confounding factors (i.e., structural lesions, abnormal preexisting cognitive and behavioral background).

2. Materials and methods

We retrospectively reviewed the clinical records and the 24-hour EEG (24-h EEG) recordings of all children referred to the Danish Epilepsy Centre in Dianalund (Denmark) between March 2003 and December 2014, with an established diagnosis of ESES or because of the clinical suspicion of ESES.

Inclusion criteria for patients with idiopathic ESES were as follows: 1) normal neurodevelopmental baseline before ESES onset, 2) normal brain magnetic resonance imaging (MRI), 3) appearance of cognitive/behavioral deterioration with or overt epileptic seizures, and 4) spike–wave index (SWI) ≥ 50% during NREM sleep in overnight EEG recording at the time of ESES diagnosis.

All patients underwent longitudinal clinical evaluations, brain MRI, at least one 24-h EEG, and at least one neuropsychological examination. Gender, perinatal and family history, psychomotor development before ESES onset, age at epilepsy onset and at ESES diagnosis, symptoms at onset and during the course of ESES, seizure types, treatments, neuroimaging results, and behavioral–cognitive–motor status were collected from patients' records and by interviewing the patients' relatives. Neuropsychological evaluations (Leiter and/or Wechsler Intelligence Scale for Children (WISC) III or IV or Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R) and/or Raven and/or (Neuropsychology): A Developmental Neuropsychological Assessment (NEPSY) I and/or Reynolds Intellectual Assessment Scales (RIAS) and/or Kuno Beller Test and/or Test of Everyday Attention for Children (TEA-Ch)) were

Table 1
Electroclinical features of our cohort.

#	Gender	Family history (epilepsy/FS)	Age at epilepsy onset (y, m)	Age at ESES onset (y, m)	ESES duration (y, m)	Seizure type	SES side and pattern	Max SWI	Neurological and cognitive impairment during ESES	Cognitive sequelae after ESES remission
1	M	−	4,6	8,3	7,7	GTC	Diffuse	96%	Behav. disord, inattentiveness, learning and language diff., enuresis	Learning diff.
2	F	−	5,5	8,4	1,1	Rolandic, secondary generalized toni-clonic (sGTC)	R hemispheric	95%	Inattentiveness, impulsivity, hyperactivity, stereotypies, learning diff., visuospatial diff.	Learning diff.
3	F	−	2,11	4	3,0	Rolandic	L focal (centro-parietal (CP))	90%	Behav disord, inattentiveness, impulsivity, hyperactivity, language diff.	Language diff.
4	M	−	5,11	8,2	1,9	Focal	L hemispheric	92%	Inattentiveness, learning and language diff.	Executive functions diff.
5	F	−	6,9	7,4	2,8	Focal, sGTC	Diffuse	75%	Behav. disord, inattentiveness, impulsivity, hyperactivity, memory impair., executive functions diff., learning and language diff.	Inattentiveness, executive functions diff.
6	M	−	6,10	7,1	0,5	Rolandic	L hemispheric	85%	Behav. disord., inattentiveness, impulsivity, hyperactivity, exec. function diff., stereotypies, learning and language diff.	Language diff.
7	F	−	3,8	3,8	3,5	Rolandic	Focal (vertex)	50%	Behav. disord., hyperactiv., learning diff., executive funct. diff., gait instability	Behav. disord., learning diff
8	M	−	−	7,8	3,6	−	L focal	65%	Behav disord, inattentiveness, impulsivity, hyperactivity, memory impair., executive funct. diff., impair. of fine and gross movements	Learning diff. (special class)
9	M	+	2,10	8,5	2,4	Rolandic	Focal (vertex)	82%	Behav. disord., inattentiveness, memory impair., executive function diff., language diff., impair of learned motor tasks	None
10	F	+	2,0	3,6	1,10	Rolandic	L hemispheric	89%	Behav, disord, inattentiveness, executive functions diff., learning and language diff., impairm of fine motor mov.	Learning diff. (special class)
11	F	−	7,7	9,8	1,6	Rolandic	R focal	65%	Behav disord, inattentiveness, impulsivity, hyperactivity executive funct. diff., learning and language diff., enuresis	ADHD (special class)
12	F	+	−	5,6	7,11	−	Multifocal (R and L)	80%	Behav. disord., inattentiveness, learning and language diff., motor impairm	Autism-like behavior
13	M	+	4,11	9,4	3,0	Rolandic	L focal (P)	81%	Behav. disord., inattentiveness, learning and language diff., motor impairm (negative myoclonus)	Language diff., behav. disord (special class)
14	M	−	5	5,5	2,8	Rolandic	Multifocal (R P and L TP)	64%	Behav. disord, moderate/severe intellectual disab., stereotypies and tics, enuresis	None
15	M	+	5	7,10	4,6	Rolandic	Multifocal (R and L)	97%	Behav. disord, inattentiveness, impulsivity, hyperactivity, executive funct and visuospatial/visuomotor diff., language diff., impairm. of fine and gross movements and balance	ADHD, learning diff (special class)
16	F	+	7,4	7,6	2,6	Absences, GTC	Diffuse	98%	Behav disord., inattentiveness, learning diff., enuresis	ESES not resolved
17	M	+	7,2	7,2	2,7	Rolandic	Multifocal (L C and L T)	80%	Behav disord., learning and language diff.	ESES not resolved
18	M	−	5	9,4	3,0	Focal	Multifocal (R and L Fr)	90%	Behav. disord., learning diff, impair. of gross motor mov.	None
19	M	−	5,2	5,4	2,10	FS, sGTC	L hemispheric	89%	Acquired aphasia (LKS), behav disord, inattentiveness, impulsivity, hyperactivity, memory impair.	Intellectual disability
20	M	−	−	8,0	2,2	−	L hemispheric	80%	Acquired aphasia (LKS), behav disord, hyperactivity	None
21	M	+	3,6	7,9	2,6	Focal	L focal (T)	>90%	Acquired aphasia (LKS), behav. disord, inattentiveness, executive funct. diff.,	Language and learning diff
22	F	−	2,8	2,11	1,3	Rolandic	Multifocal (R TPO and L TPO)	54%	Behav probl, inattentiveness, impulsivity, hyperactivity, executive funct. diff., learning diff., enuresis, motor impairm.	Learning diff, behavioral disord.
23	F	+	3,0	5,9	6,11	Rolandic	Multifocal (R and L)	89%	Behav disord., inattentiveness, learning diff	None
24	F	+	3,0	5,0	5,0	Absences	Multifocal (R and L)	94%	Behav disord., inattentiveness, language diff., visuomotor diff., impair. of fine and gross movem., enuresis	ESES not resolved

ADHD: attention-deficit/hyperactivity disorder; ESES: epileptic encephalopathy with status epilepticus during sleep; SES: status epilepticus during sleep; FS: febrile seizures; y: years; m: months; M: male; F: female; unremark: unremarkable; GTC: generalized tonic–clonic; Behav: behavioral; disord: disorders; diff: difficulties; impair: impairment; disturb: disturbances; movem: movement; Fr: frontal; T: temporal; P:parietal; O: occipital.

repeatedly performed at the time of ESES diagnosis and in the follow-up. When a formal neuropsychological evaluation was not possible because of the deterioration of cognitive status and/or patients' lack of cooperation, the cognitive assessment was based on clinical evaluation, parental reports, and information on school performances and achievements. Each patient underwent 1–10 neuropsychological examination

Table 2
Clinical features and EEG topography.

	Focal (vertex) (n = 2)	L focal (n = 4)	R focal (n = 1)	L hemisph (n = 5)	R hemisph (n = 1)	Multifocal (n = 8)	Diffuse (n = 3)
Behavioral disord	7; 9	3; 8; 13; 21	11	6; 10; 19; 20		12; 14; 15; 17; 18; 22; 23; 24	1; 5; 16
ADHD/hyperactivity	7	3; 8	11	6; 19	2	15; 22	5
Inattentiveness	9	21; 13		4; 10		12; 23; 24	1; 16
Learning diff.	7	13	11	4; 6; 10	2	12; 17; 18; 22, 23	1; 5; 16
Language diff.	9	3; 13	11	4; 6; 10		12; 15; 17; 24	1; 5
Executive funct. diff.	7; 9	8; 21	11	6; 10		15; 22	5
Visuomotor/spatial impair					2	15; 24	
Acquired aphasia		21		19; 20			
Stereotypies/tics				6	2	14	
Gait instab./balance	7					15	
Impairm motor movemen.		8; 13		10		12; 15; 18; 22; 24	
Impairm motor learned tasks	9						
Negative myoclonus		13					
Enuresis			11			14; 22; 24	1; 16

Numbers in the table indicate the corresponding patient in Table 1.

(mean: 3.4). The clinical EEG correlations were assessed analyzing the EEG features and the cognitive impairment at every EEG control. In all patients, the clinical, EEG, and neuropsychological assessments were performed at the Danish Epilepsy Centre.

Age at ESES onset was defined as the age when a SES pattern in the 24-h EEG was demonstrated for the first time in a patient with a clinical picture consistent with ESES, according to the inclusion criteria abovementioned. Age at resolution of ESES was defined as the age when a clear clinical improvement in the cognitive and behavioral domains was reported associated with a 24-h EEG recording showing the disappearance of the ESES pattern. This finding had to be confirmed in another 24-h EEG recording after at least 6 months, as in previous studies [8,15,17]. Follow-up ranged from 3 to 10 years.

2.1. EEG parameters for ESES diagnosis

Electroencephalography (EEG) was recorded by scalp electrodes placed over the scalp according to the 10–20 International system. The overnight SWI was calculated by using a semiautomated spike search method implemented in the Brain Electrical Source Analysis (BESA) software (BESA Research 6.0). Spikes were detected by template matching, in which an average of the visually identified, representative spikes for each EEG served as template. The possible influence of sleep slow waves on the accuracy of template matching was minimized by applying a 4–40-Hz zero phase band pass filter [18]. Calculation and graphical representation of the SWI was performed in a MATLAB environment (MATLAB, version 7.3.0 R2006b). Patients were divided into 3 groups, based on the SWI: 1) ≥85%, 2) 70–84%, and 3) 50–69%. The topography of the epileptiform discharges in the overnight EEG recording with the highest SWI was classified as follows: a) diffuse when sleep EEG abnormalities were bilateral; b) hemispheric when they were localized to one hemisphere without or with negligible spread to the contralateral hemisphere; c) multifocal when multiple foci either in the same hemisphere or in both hemispheres, discharging asynchronously, were observed; d) focal when the epileptic abnormalities were located in one or two lobar regions of the same hemisphere (Fig. 1) [19].

2.2. Genetics

Pathogenic variants in 78 epilepsy genes including *GRIN2A* and *CNKSR2* were screened by using a targeted next generation sequencing (NGS) gene panel. Genomic deoxyribonucleic acid (DNA) from blood was extracted using standard methods, and a NGS panel screening was performed based on the Ion Torrent SureSelect platform as previously described [20]. Variants were assumed to be pathogenic if they were nonsynonymous, splice-site altering, nonsense, or frameshift changes, not present in control samples (gnomAD — see URLs), and had arisen de novo in the patient or segregated with the disorder in the family.

3. Results

Out of 78 subjects diagnosed at the Danish Epilepsy Centre from March 2003 to December 2014 as having ESES (mean admission per year: 7.1), we collected 24 patients (30.7%) with idiopathic ESES (mean number: 2.1 per year). Gender ratio was 14 M/10 F. Mean age at ESES diagnosis was 6 years and 9 months (range: 2 years, 11 months–10 years).

3.1. Epilepsy

Family history for epilepsy was positive in nine (37.5%) subjects. One additional patient had a family history positive for a single seizure in the father. Epileptic seizures were reported in 21 (87.5%) out of 24 patients. Mean age at epilepsy onset was 4 years and 8 months (range between 2 years–7 years and 7 months). Seizure types are reported in Table 1. In 14/21 subjects, epilepsy appeared before ESES onset. Mean epilepsy duration prior to the ESES diagnosis was 2 years and 3 months (range: 2 months–5 years and 7 months). At the time of ESES onset, 6/14 did not show any change in seizure frequency and/or semiology. However, one of them started to have a new seizure type, i.e., negative myoclonus; 5/14 children showed an increment of their usual seizures; 2/14 (#18 and #9) who were seizure-free at the time of ESES onset since 17 months and 6 months, respectively, started to have again their previous seizures. In seven children (33%), seizure onset and diagnosis of ESES occurred at the same time.

During the ESES period, four children had daily/weekly seizures, five children had 1–4 seizures per year, and four presented with only 1–2 seizures during the whole ESES period (<1 seizure/year). In the remaining children, seizures frequency fluctuated, alternating periods of seizure control with periods of seizure relapse. Ten children out of the 21 with epilepsy were seizure-free on antiepileptic treatment within 1 year after ESES onset.

Three subjects (#8, #12, #20) out of 24 never had overt seizures. Patient #20 presented with a clinical picture consistent with Landau–Kleffner syndrome (LKS) with left side hemispheric EEG discharges, patient #8 showed a left hemisphere EEG focus, and patient #12 showed multifocal bilateral EEG abnormalities.

3.2. Cognitive/behavioral/motor symptoms

Encephalopathy related to status epilepticus during slow sleep onset was characterized in 16 (66.6%) patients by behavioral changes, such as appearance of aggressive behavior and difficulties in social interactions

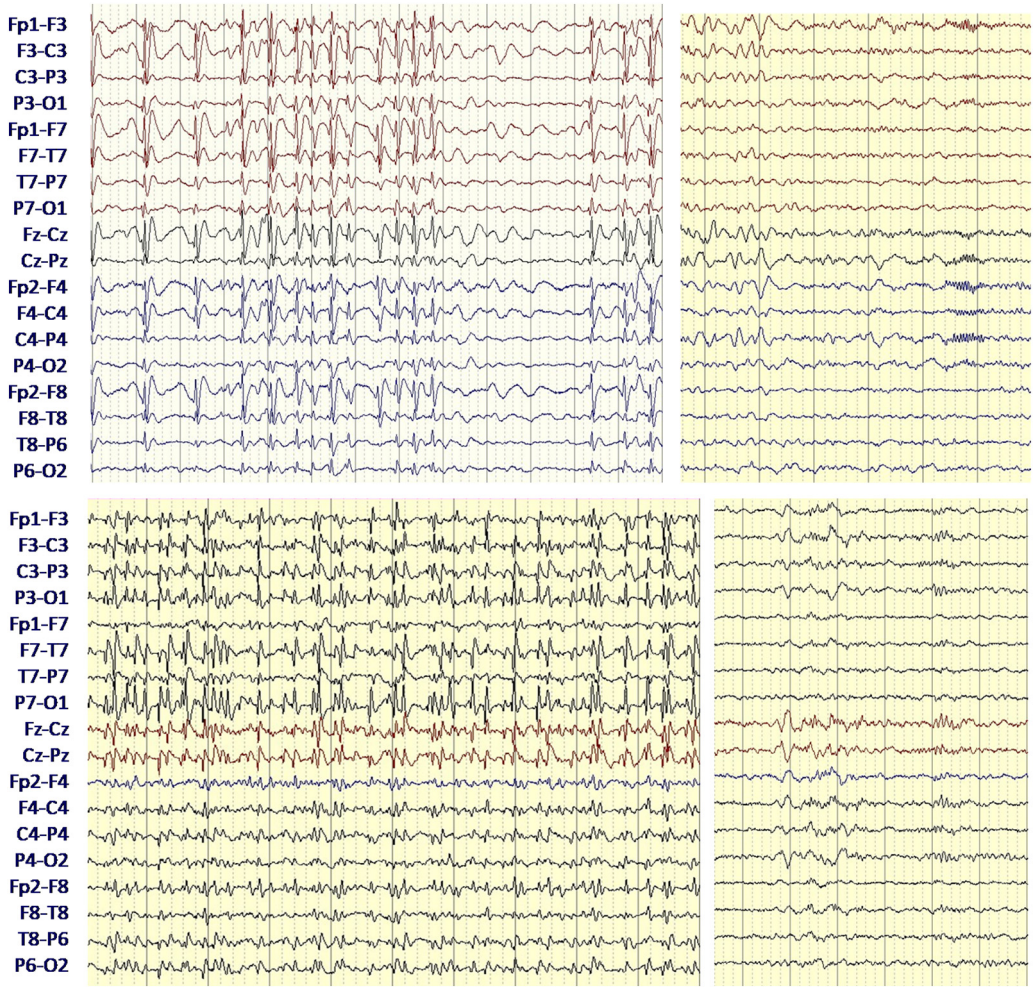

Fig. 2. Upper panel: an example of changes in the EEG in a patient with consistent electroclinical changes (observed in 11 patients). Lower panel: an example of the EEG in a patient with inconsistency between the improvement of the EEG features during NREM sleep and the fluctuations of the clinical severity, i.e., transitory cognitive and behavioral improvements (observed in 13 patients).

with peers, and in 12 (50%) patients by attention-deficit/hyperactivity disorder (ADHD) features such as attention-deficits and/or hyperactivity. Learning disabilities and language deterioration were detected since the appearance of ESES in 10 (41.6%) and in six (25%) patients, respectively, including in this latter a group of three children (#19, #20, #21) with acquired aphasia consistent with LKS. Motor disturbances were referred since the onset of ESES in 10 children (41.6%). In particular, motor dysfunctions such as postural instability and clumsiness were reported in six patients, orofacial dyspraxia with drooling in three, dyspraxia in one, negative myoclonus with sudden falls to the ground in one, and intermittent disturbance of coordination in the right limbs in one. Finally, one child presented with difficulties of word pronunciation (not otherwise specified) and gross motor hindrance and another child with nocturnal enuresis as initial symptoms of ESES.

During the course of ESES, different degrees and various combinations of behavioral disorders and ADHD features (such as inattentiveness, hyperactivity, and impulsivity) and of cognitive disturbances (such as learning and language difficulties, impairment of executive functions, memory impairment, visuomotor/visuospatial impairment) were observed in all patients. Acquired aphasia was observed in three children (#19, #20, #21) with LKS. Motor stereotypies were evident in three patients (#2, #6, #14), associated with tics in one of them (#14) (Tables 1 and 2).

3.3. Sleep EEG during ESES

On average, each child underwent 6.7 24-h EEG recordings (range: 1–13). Maximum SWI during all-night NREM sleep ranged from 50 to 98%. In 13 (54%) patients, the SWI was ≥85%; in six (25%), it was between 70 and 84%; in the remaining five (21%), SWI varied from 50 to 69%. Regarding the scalp distribution of the sleep EEG epileptiform discharges, at the time of maximum SWI, they were diffuse in three patients, left hemispheric in five, right hemispheric in one, focal in the left hemisphere in four, focal in the right hemisphere in one, focal over the vertex in two, and multifocal in eight (Table 1). It is worth to mention however, that throughout the evolution of ESES, considerable variations of the topography and diffusion patterns of the EEG epileptiform discharges could occur in the same child.

3.4. Clinical EEG correlation

In 14 patients, we noticed a constant parallel between the severity of the clinical picture and the SWI, i.e., the worsening of the clinical picture was associated with an increment of the SWI. In 10 patients (#4, #8, #9, #12, #13, #15, #16, #18, #22, #23), in some periods of their clinical history, these relationships were less clear, since fluctuations of the clinical severity, i.e., transitory improvements in cognition and behavior, were inconstantly paralleled by variations (i.e., decrease) of SWI (Fig. 2). In

3 patients (#8, #9, #22), some clinical symptoms (inattentiveness in patient #8, memory in patient #9, motor symptoms in patient #22) fluctuated in parallel with SWI whereas the other clinical manifestations were quite independent from SWI.

Table 2 shows that a heterogeneous pattern of behavioral disorders, ADHD features (inattentiveness, impulsivity, hyperactivity), learning and language difficulties, and difficulties of executive functions affected all children without a strict correlation with SES side and topography at the SWI peak. In addition, visuomotor/spatial impairment was observed in three children, two (#15, #24) with bilateral multifocal abnormalities and one (#2) with right hemispheric SES. Motor dysfunctions such as impairment of fine and gross motor movements were observed in children with multifocal SES (patients #12, #15,#18, #22, #24), left focal SES (#8, #13), or left hemispheric (#10) SES. Other disturbances such as gait instability, negative myoclonus, and impairment of learned motor tasks were observed more rarely, affecting only one or two children. Stereotypies and tics were reported in three children with multifocal (#14), right (#2), or left hemispheric (#6) SES. Enuresis was reported in six children with diffuse (#1, #16) or multifocal (#14, #22, #24) SES, and only in one with lateralized right focal SES (#11) (see Tables 1 and 2).

Acquired aphasia consistent with the diagnosis of LKS was observed in three children with left hemispheric SES (#19, #20) or left focal SES (#21).

3.5. Genetics

We screened 13 of the 24 patients for pathogenic gene variants. In two patients (#12, #24) (15%), we found a presumed disease causing variant in *GRIN2A*, c.172G>T, p.Glu58Ter, and c.2007 + 1G>A, IVS7. Both variants/patients have been previously published [3,21]. Segregation analysis revealed that both variants were paternally inherited, and both fathers had epilepsy during childhood. Both have been seizure-free and off medication for many years. No pathogenic variants were observed in *CNKSR2*.

3.6. Therapy

In our cohort, a mean of 2.5 antiepileptic drugs (AEDs) per patient (range: 1–4) was used, including clobazam (CLB), ethosuximide (ETS), valproate (VPA), sulthiame (STM), lamotrigine (LTG), and levetiracetam (LEV). Cycles of prednisolone (PRD) were performed in 10/12 patients with a maximum benefit duration of one year. Two patients whose seizures did not respond to AEDs (#1, #19) were treated with ketogenic diet (KD) with clinical improvement.

3.7. Outcome

Twenty-one (87.5%) patients had achieved ESES remission at the last follow-up. In these patients, mean ESES duration was 3 years and 1 month (range: 0.5–7 years and 11 months), and mean age at remission was 14 years and 3 months (range: 4 years and 2 months–15 years and 10 months). Three subjects were still presenting with ESES. Their mean age was 10 years–5 months (range: 9 years and 9 months–11 years and 6 months).

Out of the 21 patients in whom ESES was resolved, a complete cognitive and behavioral recovery was observed in five (23.8%) (see Table 1). They had a mean ESES duration of 3 years and 6 months (range: 2 years and 2 months–6 years and 11 months) and SWI index during the most active phase ranging from 64% to 90%. Mean age at ESES onset was 7 years and 4 months (range: 5 years, 5 months–9 years, 4 months). Their seizures were treated with STM and/or PRD.

In 13 patients, minor/moderate residual disabilities persisted (12 children showed learning difficulties, language problems and disorders in executive functions; residual behavioral disorders persisted in five — see Table 1). In this group of subjects, mean duration of ESES was 3 years and 2 months (range: 12 months–7 years, 11 months). Mean age at ESES onset was 6 years and 7 months (range: 2 years, 11 months–9 years, 4 months).

Three patients (#7, #11, #19) continued to show major residual learning disabilities and behavioral disorders (see Table 1). In these patients, mean ESES duration was 2 years and 6 months (range: 1 year and 6 months–3 years and 5 months) and mean age at ESES onset was 6 years, 4 months (range: 3 years, 8 months–9 years, 8 months). The SWI was 50% in patient #7, 65% in patient #11, and 89% in patient #19. Patient #11 showed seizures that were treated with STM as add-on to VPA (after discontinuation of LTG) with partial benefit. Patient #7 showed seizures that were treated with LEV without benefit (after discontinuation of LTG, received before ESES onset), and patient #19 experienced seizures that were refractory to AEDs (STM, LEV), PRD, and KD (he already received oxcarbazepine, VPA, LTG, and CLB for seizure control before ESES onset).

4. Discussion

In this retrospective study, we have investigated the electroclinical features and long-term evolution of a homogeneous cohort of children with idiopathic ESES. A distinctive feature of our study is the longitudinal EEG and neuropsychological assessment, with repeated overnight EEGs and, in most of the children, repeated neuropsychological evaluations. In addition, in a subset of patients, we have explored the genetic background.

In our group of patients, epileptic seizures were a common feature, however 3/24 (12,5%) children never had overt seizures. Heterogeneous seizure types were reported, such as absences, generalized tonic–clonic seizures, focal seizures, including Rolandic seizures that were detected in more than 60% of the patients with epilepsy. Epilepsy appeared before the onset of ESES in about 60% of patients with epilepsy whereas in the remaining 40%, the onset of epileptic seizures was concomitant with the detection of SES and with the recognition of a cognitive and behavioral deterioration. In patients with epilepsy before ESES onset, the appearance of ESES was not accompanied by changes in seizure frequency or semiology in about 50% of them (even though one of them started to present with negative myoclonus as a new seizure type), whereas the remaining subjects showed an increase of seizure frequency or reappearance of seizures after a seizure-free period. Our findings differ from the observation of Saltik et al. [15] in a group of children with idiopathic focal epilepsy evolving to ESES, who reported at ESES onset an increment of seizure frequency and/or appearance of new seizure types in more than 90% of subjects. Therefore, our results may suggest that changes in seizure frequency or semiology, although possibly useful to suspect the onset of ESES, might not be such a sensitive marker as previously suggested [15]. In addition, 13% of children in our cohort never experienced overt seizures, a percentage higher than in previous series of patients with ESES [8,9,22]. This might depend both on different referral policies for a 24-h EEG (patients with suspicion of ESES without occurrence of seizures are referred to our center) and on our inclusion criteria that selected only patients with idiopathic ESES, at variance with other studies that included children with both idiopathic and symptomatic etiologies, these latter more prone to develop epilepsy [8,9,22]. Moreover, our series included children with LKS, which are commonly reported to have a lower incidence of a lower incidence of seizures [23]. These findings should prompt clinicians to consider the possibility of ESES and eventually to perform the proper diagnostic assessment (i.e., overnight sleep EEG or at least, EEG during a full sleep cycle) even in the absence of epileptic seizures in children with recent onset of neurobehavioral disturbances.

In our series, onset of ESES was heralded by the appearance of behavioral disorders (in particular, difficulties in social interactions, aggressivity) and/or ADHD features in 66.6% and 50% of children, respectively. This is similar to Saltik et al.'s report [15], who described behavioral disturbances at ESES onset in about 80% of subjects. In

addition, we observed learning disabilities, including language deterioration, and motor disturbances at ESES onset in about 65% and 40% of children, respectively. Overall, in all children, the appearance of one or more of a various combination of these disturbances characterized the onset of ESES. Our results further reaffirm the concept that the appearance of cognitive and/or behavioral disturbances, in concomitance with the epilepsy onset or during the course of an idiopathic epilepsy, should warn on the possible diagnosis of ESES.

During the course of ESES, a heterogeneous pattern of cognitive derangement and behavioral disorders was observed in association with different types of motor dysfunctions. Behavioral disorders and cognitive derangements have been reported in nearly all cases with ESES [2,24,25]; indeed, they are the ESES features with the most severe long-term consequences [8,16,26,27]. These disturbances have been reported to vary from mild to severe and can include language deterioration, temporospatial impairment, aggressiveness, impulsivity, inattentiveness, hyperactivity, learning difficulties, and communication problems; in some cases, psychotic features have been reported [2].

In our series, cognitive disturbances (such as learning and language difficulties, impairment of executive functions, memory impairment, visuomotor/visuospatial impairment) combined with ADHD features were observed in all patients, independently from the topography of the SES epileptiform discharges. In fact, at variance with previous reports [2,28,29], in about one-half of patients, we could not find a constant correlation between the pattern of cognitive/behavioral derangement and the topography and side of SES. Several explanations may account for these discrepancies. First, the topography of the epileptiform activity could vary in the same patient during the course of ESES. Moreover, it was not always possible to have the neuropsychological assessment in parallel with the EEG evaluation, because of the severity of the cognitive/behavioral status. Second, beside the SWI and the EEG topography, we should also take into consideration some qualitative EEG parameters, e.g., the morphology of the epileptiform discharges, as well as the sleep–wake distribution of the epileptiform abnormalities during the evolution of SES. Third, recent data have shown in ESES an impairment of the sleep physiologic homeostatic processes, which subserve local plastic changes associated with cognitive functions in developmental age, more pronounced at the site of the epileptic focus but affecting as well cortical areas distant from it [30,31]. Therefore, it can be hypothesized that the pattern of neuropsychological/behavioral derangement may depend on altered sleep homeostasis, due to persistent epileptic activity, in cortical areas beyond the epileptic focus [32,33]. Fourth, in patients with focal SES, i.e., with epileptic activity restricted to one or two lobar regions, the associated cognitive deficits might be quite selective and might be even overlooked on clinical grounds, and possibly not properly investigated by standard neuropsychological evaluations, rendering the description of the clinical picture incomplete, thus preventing precise clinical EEG correlations [34–36].

Recent genetic data have shown a possible association between *GRIN2A* and *CNKSR2* pathogenic variants and conditions, such as Rolandic epilepsy, LKS, or ESES, encompassed in the epilepsy–aphasia spectrum disorders (EASD) [3–7,37]. In our study, we found two patients out of 13 (15.4%) with a pathogenic *GRIN2A* variant, and none with *CNKSR2*. This finding is in agreement with previous reports that have estimated that up to 20% of patients with EASD have a pathogenic variant in *GRIN2A* [3–5].

Complete recovery from ESES was achieved only in 23% of children whereas minor/moderate dysfunctions persisted in 62% and major disabilities in 15% of patients. Although the idiopathic etiology has been suggested as one of the factors possibly related to a good prognosis [8], complete recovery in our cohort was obtained only in less than one-fourth of children, a worrisome observation considering that all these children were neurologically, cognitively, and behaviorally healthy before ESES. A recent study has shown that children with early-onset idiopathic ESES were the most vulnerable in terms of neuropsychological outcome as compared with those with a later onset [16]. Our data are in agreement with these findings showing an earlier age of ESES onset (mean age: 6 months, 4 years) in the children with the most severe sequelae as compared with those who completely recovered after ESES (mean age at ESES onset: 7 years, 4 months). We did not observe any correlation neither between the SWI and the cognitive outcome (mean SWI was 81% in the completely recovered group versus 61% in the group with major sequelae) nor between ESES duration and cognitive outcome (mean: 3 years–4 months in the recovered group versus 2 years–7 months in the more impaired group). This latter result is not concordant with previous findings showing that a longer duration of ESES could predict a worse outcome [24,38]. These observations emphasize once again one of the most puzzling issues related to ESES, i.e., how prolonged epileptic activity during sleep (SES) can significantly and often permanently affect the cognitive and behavioral outcome of these children. In recent years, it has been proposed that persistent sleep-related epileptic activity might impair the physiological homeostatic processes that occur during sleep and that are particularly relevant in the developmental age [32,33]. Sleep ensures synaptic homeostasis by promoting synaptic depression and renormalization, memory consolidation, and cellular recovery after the increase of synaptic strength that occurs during wakefulness [39]. The extreme activation of spike–wave activity during slow-wave sleep, every night for months or years, in children with ESES would be expected to impair the physiologic sleep homeostatic processes. The analysis of the changes of the slope of sleep slow-wave activity (SSWA) can provide a measure of changes in synaptic strength and associated sleep homeostasis [40,41]. It has been shown that in children having ESES, the slope of SSWA did not change across the night, as if the homeostatic recovery of sleep was impaired [30]. In the developmental age, during which cortical maturation (through massive synaptogenesis, synaptic pruning, and refinement of synaptic circuits) takes place [42–44], a systematic spike-induced disruption of synaptic renormalization during NREM sleep would produce severe, possibly permanent changes in cortical wiring, that could result clinically in the cognitive and behavioral disorders observed in ESES.

To lend support to this hypothesis, recently, Bolsterli et al. have shown in children with idiopathic ESES that the cognitive/behavioral outcome might correlate with the degree of impairment of the physiological homeostatic processes occurring during sleep [45]. Indeed, the complete cognitive/behavioral recovery after ESES was observed in those children in whom sleep homeostasis, as measured by the analysis of the slope of SSWA, was partially preserved during sleep during active phase of ESES. On the contrary, severe perturbation of SSWA during ESES active phase was associated with the worst neuropsychological sequelae. These latter findings suggest that, besides SWI and spike topography, the analysis of sleep EEG features (i.e., quantification and modification of SSWA) should be included in the parameters to be investigated for clinical EEG correlations in ESES, with possible prognostic significance. In addition, they might be relevant to comprehend the role of impaired sleep homeostasis in the cognitive derangement occurring in ESES. Finally, another factor that in our cohort presumably played a role in the outcome was the response to therapy, which was a distinguished feature between the children who completely recovered after ESES and those who continued to present neuropsychological disorders. In fact, the response to therapy resulted in periods in which the subjects had an electroclinical improvement. Thus, it seems reasonable to think that patients whose seizures did not respond to therapy were also those patients who had less “free-periods”, thus having a more prolonged and continuous SES-related damage.

5. Conclusion

Our study was focused on patients with idiopathic ESES, who experienced an abrupt cognitive and behavioral decline, in the absence of significant changes in seizure frequency or type. In addition, the contribution of possible confounding factors due to preexistent or concomitant

pathologies in determining the encephalopathy was excluded, hence, our definition of idiopathic ESES as a "pure" condition. We suggest that idiopathic ESES is an optimal model of epileptic encephalopathy resulting from the harmful effect in the developmental age of protracted "interictal" sleep-related epileptiform activity on the local plastic changes associated with learning and other cognitive functions that physiologically occur during sleep [45], in previously healthy children. This hypothesis should be tested not only in ESES but also in a larger population of childhood epilepsies with significant activation of focal paroxysmal activity during sleep. Future lines of research should investigate whether children with epilepsy displaying high SWI during sleep and minor or absence of cognitive disorders show minimally impaired or normal reduction of the slope of SSWA, thus reflecting a minimal perturbance or preservation of synaptic renormalization. For this scope, the use of novel EEG parameters, in addition to SWI, such as the decline of slow-wave slopes in NREM sleep, coupled with new neuroimaging techniques (such as diffusion tensor imaging tractography, functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), Magnetoencephalography (MEG)) and sophisticated neuropsychological and behavioral tools tailored to detect selective or subtle cognitive dysfunctions, in particular in children with focal ESES, might allow a timely diagnosis and treatment and might shed light on the cortical networks underlying specific cognitive functions.

Author contributions

EP, EG, and GR contributed to the conception, design of the work, collection/analysis/interpretation of the data, and produced the manuscript drafts. RSM, MN, MSK, and PS contributed to the acquisition of the data and data analysis. SB contributed to the collection of the EEG data.

All authors have been responsible in critically appraising the work and approving the final version.

Declaration of Competing Interest

The authors declared no conflicts of interest.

Acknowledgments

We are indebted to the families of the children for their collaboration in performing this study.

Funding

This work was supported by the Lennart Gram Fonden to GR.

Ethics approval and consent

All probands or, in case of minors, their parents or legal guardians, gave informed consent. Approval from the local ethical committee was obtained.

References

[1] Patry G, Lyagoubi S, Tassinari CA. Subclinical "electrical status epilepticus" induced by sleep in children. A clinical and electroencephalographic study of six cases. Arch Neurol 1971;24:242–52.
[2] Tassinari CA, Cantalupo G, Dalla Bernardina B, Darra F, Bureau M, Cirelli C, et al. Encephalopathy related to status epilepticus during slow sleep (ESES) including Landau–Kleffner syndrome. In: Bureau M, Genton P, Dravet C, Delgado-Escueta A, Tassinari CA, Thomas P, Wolf P, editors. Epileptic syndromes in infancy, childhood and adolescence. 5th ed. John Libbey Eurotext Ltd.; 2012. p. 255–75.
[3] Lemke JR, Lal D, Reinthaler EM, Steiner I, Nothnagel M, Alber M, et al. Mutations in GRIN2A cause idiopathic focal epilepsy with Rolandic spikes. Nat Genet 2013;45:1067–72.
[4] Carvill GL, Regan BM, Yendle SC, O'Roak BJ, Lozovaya N, Bruneau N, et al. GRIN2A mutations cause epilepsy-aphasia spectrum disorders. Nat Genet 2013;45:1073–6.
[5] Lesca G, Rudolf G, Bruneau N, Lozovaya N, Labalme A, Boutry-Kryza N, et al. GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. Nat Genet 2013;45:1061–6.
[6] Vaags AK, Bowdin S, Smith ML, Gilbert-Dussardier B, Brocke-Holmefjord KS, Sinopoli K, et al. Absent CNKSR2 causes seizures and intellectual, attention, and language deficits. Ann Neurol 2014;76:758–64.
[7] Damiano JA, Burgess R, Kivity S, Lerman-Sagie T, Afawi Z, Scheffer IE, et al. Frequency of CNKSR2 mutation in the X-linked epilepsy–aphasia spectrum. Epilepsia 2017;58:e40–3.
[8] Caraballo RH, Veggiotti P, Kaltenmeier MC, Piazza E, Gamboni B, Lopez Avaria MF, et al. Encephalopathy with status epilepticus during sleep or continuous spikes and waves during slow sleep syndrome: a multicenter, long-term follow-up study of 117 patients. Epilepsy Res 2013;105:164–73.
[9] Fernández IS, Peters J, Takeoka M, Rotenberg A, Prabhu S, Gregas M, et al. Patients with electrical status epilepticus in sleep share similar clinical features regardless of their focal or generalized sleep potentiation of epileptiform activity. J Child Neurol 2013;28:83–9.
[10] Liukkonen E, Kantola-Sorsa E, Paetau R, Gaily E, Peltola M, Granström ML. Long-term outcome of 32 children with encephalopathy with status epilepticus during sleep, or ESES syndrome. Epilepsia 2010;51:2023–32.
[11] Raha S, Shah U, Udani V. Neurocognitive and neurobehavioral disabilities in epilepsy with electrical status epilepticus in slow sleep (ESES) and related syndromes. Epilepsy Behav 2012;25:381–5.
[12] Margari L, Buttiglione M, Legrottaglie AR, Presicci A, Craig F, Curatolo P. Neuropsychiatric impairment in children with continuous spikes and waves during slow sleep: a long-term follow-up study. Epilepsy Behav 2012;25:558–62.
[13] Praline J, Hommet C, Barthez MA, Brault F, Perrier D, Passage GD, et al. Outcome at adulthood of the continuous spike–waves during slow sleep and Landau–Kleffner syndromes. Epilepsia 2003;44:1434–40.
[14] Arhan E, Serdaroglu A, Aydin K, Hırfanoglu T, Soysal AS. Epileptic encephalopathy with electrical status epilepticus: an electroclinical study of 59 patients. Seizure 2015;26:86–93.
[15] Saltik S, Uluduz D, Cokar O, Demirbilek V, Dervent A. A clinical and EEG study on idiopathic partial epilepsies with evolution into ESES spectrum disorders. Epilepsia 2005;46:524–33.
[16] De Giorgis V, Filippini M, Macasaet JA, Masnada S, Veggiotti P. Neurobehavioral consequences of continuous spike and waves during slow sleep (CSWS) in a pediatric population: a pattern of developmental hindrance. Epilepsy Behav 2017;74:1–9.
[17] Galanopolou A, Bjko A, Lado F, Moshe' SL. The spectrum of neuropsychiatric abnormalities associated with electrical status epilepticus in sleep. Brain and Development 2000;22:279–95.
[18] Larsson PG, Wilson J, Eeg-Olofsson O. A new method for quantification and assessment of epileptiform activity in EEG with special reference to focal nocturnal epileptiform activity. Brain Topogr 2009;22:52–9.
[19] Gardella E, Cantalupo G, Larsson PG, Fontana E, Dalla Bernardina B, Rubboli G, et al. EEG features in encephalopathy with status epilepticus during slow sleep. Epileptic Disord 2019 [in press].
[20] Møller RS, Wuttke TV, Helbig I, Marini C, Johannesen KM, Brilstra EH, et al. Mutations in GABRB3: from febrile seizures to epileptic encephalopathies. Neurology 2017;88:483–92.
[21] von Stülpnagel C, Ensslen M, Møller RS, Pal DK, Masnada S, Veggiotti P, et al. Epilepsy in patients with GRIN2A alterations: genetics, neurodevelopment, epileptic phenotype and response to anticonvulsive drugs. Eur J Paediatr Neurol 2017;21:530–41.
[22] Fortini S, Corredera L, Pastrana AL, Reyes G, Fasulo L, Caraballo RH. Encephalopathy with hemi-status epilepticus during sleep or hemi-continuous spikes and waves during slow sleep syndrome: a study of 21 patients. Seizure 2013;22:565–71.
[23] Caraballo RH, Cejas N, Chamorro N, Kaltenmeier MC, Fortini S, Soprano AM. Landau–Kleffner syndrome: a study of 29 patients. Seizure 2014;23:98–104.
[24] Bureau M. Continuous spikes and waves during slow sleep (CSWS): definition of the syndrome. In: Beaumanoir A, Bureau M, Deonna T, Mira L, Tassinari CA, editors. Continuous spikes and waves during slow sleep: acquired epileptic aphasia and related conditions. London, UK: John Libbey; 1995. p. 17–26.
[25] Jayakar PB, Seshia SS. Electrical status epilepticus during slow-wave sleep: a review. J Clin Neurophysiol 1991;8:299–311.
[26] Boel M, Casaer P. Continuous spikes and waves during slow sleep: a 30 months follow-up study of neuropsychological recovery and EEG findings. Neuropediatrics 1989;20:176–80.
[27] Seegmüller C, Deonna T, Dubois CM, Valenti-Hirsch MP, Hirsch E, Metz-Lutz MN, et al. Long-term outcome after cognitive and behavioral regression in nonlesional epilepsy with continuous spike-waves during slow-wave sleep. Epilepsia 2012;53:1067–76.
[28] Scholtes FB, Hendriks MP, Renier WO. Cognitive deterioration and electrical status epilepticus during slow sleep. Epilepsy Behav 2005;6:167–73.
[29] Pera MC, Brazzo D, Altieri N, Balottin U, Veggiotti P. Long-term evolution of neuropsychological competences in encephalopathy with status epilepticus during sleep: a variable prognosis. Epilepsia 2013;54 Suppl 7:77–85.
[30] Bölsterli BK, Schmitt B, Bast T, Critelli H, Heinzle J, Jenni OG, et al. Impaired slow wave sleep downscaling in encephalopathy with status epilepticus during sleep (ESES). Clin Neurophysiol 2011;122:1779–87.
[31] Bölsterli Heinzle BK, Fattinger S, Kurth S, Lebourgeois MK, Ringli M, Bast T, et al. Spike wave location and density disturb sleep slow waves in patients with CSWS (continuous spike waves during sleep). Epilepsia 2014;55:584–91.
[32] Tassinari CA, Rubboli G. Cognition and paroxysmal EEG activities: from a single spike to electrical status epilepticus during sleep. Epilepsia 2006;47(Suppl. 2):40–3.

[33] Rubboli G, Huber R, Tononi G, Tassinari CA. Encephalopathy related to status epilepticus during sleep: a link with sleep homeostasis? Epileptic disorders; 2019 [in press].
[34] Kuki I, Kawawaki H, Okazaki S, Ikeda H, Tomiwa K. Epileptic encephalopathy with continuous spikes and waves in the occipito-temporal region during slow-wave sleep in two patients with acquired Kanji dysgraphia. Epileptic Disord 2014;16:540–5.
[35] Eriksson K, Kylliäinen A, Hirvonen K, Nieminen P, Koivikko M. Visual agnosia in a child with non-lesional occipito-temporal CSWS. Brain and Development 2003;25:262–7.
[36] Tassinari CA, Cantalupo G, Rubboli G. Focal ESES as a selective focal brain dysfunction: a challenge for clinicians, an opportunity for cognitive neuroscientists. Epileptic Disord 2015;17:345–7.
[37] Bobbili DR, Lal D, May P, Reinthaler EM, Jabbari K, Thiele H, et al. Exome-wide analysis of mutational burden in patients with typical and atypical Rolandic epilepsy. Eur J Hum Genet 2018;26:258–64.
[38] De Negri M. Electrical status epilepticus during sleep (ESES). Different clinical syndromes: towards a unifying view? Brain and Development 1997;19:447–51.
[39] Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 2014;81:12–34.
[40] Esser SK, Hill SL, Tononi G. Sleep homeostasis and cortical synchronization: I. Modeling the effects of synaptic strength on sleep slow waves. Sleep 2007;30:1617–30.
[41] Riedner BA, Vyazovskiy VV, Huber R, Massimini M, Esser S, Murphy M, et al. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. Sleep 2007;30:1643–57.
[42] Huttenlocher PR. Synaptic density in human frontal cortex — developmental changes and effects of aging. Brain Res 1979;163:195–205.
[43] Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 1997;387:167–78.
[44] Petanjek Z, Judaš M, Šimic G, Rasin MR, Uylings HB, Rakic P, et al. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. Proc Natl Acad Sci U S A 2011;108:13281–6.
[45] Bölsterli BK, Gardella E, Pavlidis E, Wehrle FM, Tassinari CA, Huber R, et al. Remission of encephalopathy with status epilepticus (ESES) during sleep renormalizes regulation of slow wave sleep. Epilepsia 2017;58:1892–901.