Original article

Epileptic Disord 2020; 22 (1): 39-54

Surgical management of pediatric patients with encephalopathy due to electrical status epilepticus during sleep (ESES)

Shelly Wang [1], Alexander G. Weil [2], George M. Ibrahim [3], Aria Fallah [4], Brandon Korman [5], John Ragheb [1], Sanjiv Bhatia [1], Michael Duchowny [6]

[1] Division of Neurosurgery, Department of Surgery, Nicklaus Children's Hospital, Miami, USA
[2] Division of Neurosurgery, CHU Sainte-Justine Hospital, University of Montreal, Montreal, Canada
[3] Division of Neurosurgery, Department of Surgery, Hospital for Sick Children, University of Toronto, Toronto, Canada
[4] Division of Neurosurgery, Department of Surgery, Mattel Children's Hospital, David Geffen School of Medicine, UCLA, Los Angeles, USA
[5] Department of Pediatrics, Nicklaus Children's Hospital, Miami, USA
[6] Division of Pediatric Neurology, Nicklaus Children's Hospital, Miami, USA

Received July 19, 2019; Accepted November 16, 2019

ABSTRACT – *Aims*. ESES is a developmental epileptic disorder directly responsible for progressive encephalopathy and neurocognitive regression. The natural history, indications for surgical intervention, and predictors for favorable seizure and neuropsychological outcome remain unclear.

Methods. We performed a retrospective review of children who underwent resective or disconnective surgery for ESES between January 2009 and July 2016 at a large tertiary pediatric center. Information on the patients' demographics, seizure semiology, radiographic and electrographic findings, and surgical management was collected. The primary outcome was seizure freedom at last follow-up visit, and secondary outcomes were neuropsychological improvement and electrographic ESES resolution.

Results. We identified 11 children who underwent surgery for ESES. The mean ages were 3.2 years for seizure onset, 7.1 years for formal ESES diagnosis, and 9.4 years for surgery. Seizure etiologies included cortical malformations (four patients), encephalomalacia and gliosis from prior hemorrhage or tumor resections (three patients), developmental porencephaly (one patient), and Rasmussen's encephalitis (one patient); the etiology was unknown in two children. Preoperatively, nine children had motor deficits, seven had speech and language delay, and three had visual field defects. All children had seizures and neuropsychological regression prior to surgical consideration. Focal cortical resections were performed

Correspondence:
Nicklaus Children's Hospital,
Division of Pediatric Neurology,
Miami, USA
<michael.duchowny@mch.com>

doi:10.1684/epd.2020.1129

in seven children, and hemispherectomies in four. Post-operatively, nine children experienced decreased seizure frequency, eight had neuropsychological improvement, and nine had resolution of electrographic ESES. Patients with poor surgical outcomes had more significant pre-operative comorbidities, in addition to bilateral ESES activity.
Conclusion. In this case series, surgery for a carefully selected group of children with ESES is safe and feasible, yielding rates of seizure freedom and neuropsychological improvement that compare favorably with previous reports for antiepileptic drugs, benzodiazepines, and steroids. As we gain greater understanding into the management of ESES, surgery is an increasingly useful tool for patients with mild or moderate neurodevelopmental delay, focal epileptogenic foci, and hemi-ESES electrographic findings.

Key words: electrical status epilepticus during sleep, epilepsy, focal cortical dysplasia, Landau-Kleffner syndrome, encephalomalacia, epilepsy surgery

Electrical status epilepticus during sleep (ESES), also known as continuous spike-wave discharges during slow-wave sleep (CSWSS), is an age-dependent epileptic encephalopathy that often remits over time (Patry *et al*., 1971; Kramer *et al*., 2009; Rubboli and Tassinari, 2019). Defined by the Commission on Classification and Terminology of the International League Against Epilepsy 1989, it typically presents in children around five years of age, with clinical seizures which progress within two years to a severe epileptic encephalopathy. In addition to epileptic seizures, the onset of ESES is associated with a progressive encephalopathy characterized by developmental regression, neurobehavioral disorder and severe deficits in language, social skills, memory, global intellect and motor function (Galanopoulou *et al*., 2000; Tassinari *et al*., 2000; Veggiotti *et al*., 2001; Raha *et al*., 2012; Tassinari and Rubboli, 2019). Landau-Kleffner syndrome (LKS) is a closely related entity that involves compromised eloquent language development and typically presents with verbal language delay (Pal *et al*., 2016).

ESES limited to one cerebral hemisphere is referred to as hemi-ESES. Therapy is similarly directed towards eliminating the electrographic pattern in order to control seizures and halt neurocognitive decline. Medical management options include antiepileptic drugs (AEDs), high-dose corticosteroids, benzodiazepines, intravenous gamma globulins and the ketogenic diet (Aeby *et al*., 2005; Kramer *et al*., 2009; Caraballo *et al*., 2011; Fejerman *et al*., 2012; Veggiotti *et al*., 2012; Arzimanoglou and Cross, 2019; Jansen *et al*., 2019).

Surgery is a promising therapeutic option for pharmaco-resistant ESES, but is infrequently employed due to potential spontaneous remission of ESES, and concerns about surgical complications. Multiple subpial transections (MSTs) have been performed on patients with language-eloquent ESES in LKS, but the results are inconsistent. Focal resections and hemispherectomies are performed more rarely and yield variable results. Since the natural history of ESES and the predictors of surgical success are unclear, there is significant clinical equipoise on the optimal approach for children with this condition.

We report a cohort of children with seizures and electrographic findings of ESES who were evaluated and managed at a single tertiary center specializing in epilepsy. We herein describe the patient population including seizure semiology, radiographic findings, and neuropsychological assessment. Furthermore, we describe the factors influencing the decision to perform surgery, and report the safety and efficacy of surgical management. Lastly, we discuss the benefits of surgery compared to medical management, and describe patient factors predicting optimal outcome. Although other authors have reported small case series with resective procedures (*table 1*), to our knowledge, this is the largest case series with resective and disconnective surgical management for ESES reported to date.

Materials and methods

We performed a retrospective case review of consecutive patients undergoing surgery for ESES at Nicklaus (formerly known as Miami) Children's Hospital between January 2009 and July 2016. Patient demographic information, seizure semiology and frequency, pre-operative radiography, electrophysiology, and neuropsychological testing were evaluated. Information on the type of surgery, final surgical pathology, and any associated surgical complications were collected. At least two years of post-surgical follow-up was obtained in all patients, and post-operative follow-up was reviewed for seizure frequency, neurocognitive outcome, and academic performance. When available, a post-operative electroencephalogram (EEG) was also reviewed to determine resolution of ESES electrographic patterns.

Table 1. Literature review of case series involving children with electrical status epilepticus during sleep (ESES) who underwent resective or disconnective surgical management.

Author, year	Sample size	Etiology	Procedure	*n* (%) seizure-free	*n* (%) improved neurocognitive outcome	*n* (%) ESES electrographic resolution
Jeong *et al.*, 2017	9	PMG (4) Perinatal infarct (3) FCD (1) HME (1)	Hemispherotomy	9 (100%)	6 (66%)	6 of 6 available (100%)
Peltola *et al.*, 2011	13	Thalamic infarct (7) PMG (6)	Corpus callosotomy (9) Hemispherotomy (2) Focal resection (2)	4 of 13 overall (31%) 2 of 3 resective (66.7%)	12 (92%)	11 reduced strength and propagation of ESES
Vigliano *et al.*, 2010	1	PMG	Hemispherotomy	1 (100%)	1 (100%)	N/A
Battaglia *et al.*, 2009	2	Perinatal infarct (1) Porencephaly (1)	Hemispherectomy	2 (100%)	2 (100%)	2 (100%)
Kallay *et al.*, 2009	1	Perinatal infarct (1)	Hemispherectomy	1 (100%)	1 (100%)	1 (100%)
Loddenkemper *et al.*, 2009	8	Perinatal infarct (7) MCD (1)	Hemispherectomy (6) Focal resection (2)	6 of 8 overall (75%) 2 of 2 resective (100%)	8 (100%)	8 (100%)
Bahi-Buisson *et al.*, 2006	1	Ulegyria and periventricular leukomalacia	Hemispherectomy	1 (100%)	1 (100%)	0
Guzzetta *et al.*, 2005	1	Perinatal infarct (1)	Focal resection (1)	1 (100%)	0	1 (100%)
Roulet-Perez *et al.*, 1998	1	FCD and LKS	Focal resection	1 (100%)	1 (100%)	0
Sawhney *et al.*, 1995	21	FCD (6) Rasmussen's encephalitis (6) Non-specific gliosis (5) LKS (3) Tumor (1)	MST (21) +/- Focal resection (12)	11 (61%)	3 (17%)	N/A
Nass *et al.*, 1993	1	Tumor	Focal resection	1 (100%)	1 (100%)	N/A

ESES: electrical status epilepticus during sleep; LKS: Landau-Kleffner Syndrome; MCD: malformation cortical development; MST: multiple subpial transection; N/A: not applicable; PMG: polymicrogyria.

Inclusion criteria

Between January 2009 and July 2016, the prospectively collected data for all patients undergoing video electroencephalography (VEEG) and epilepsy workup at Nicklaus Children's Hospital were reviewed. Patients were classified with ESES if they presented with the typical EEG findings of continuous spike-waves during at least 85% of slow wave (non-REM) sleep, usually noted after seizure onset and persisting on at least three or more recordings over a period of at least one month in association with epilepsy, neuropsychological and/or motor impairment. From this cohort, we identified patients with electrographic abnormalities that were either hemi-ESES, or asymmetrically prominent in one hemisphere. Patients in this cohort were boys and girls between 0-18 years of age, who ultimately underwent surgery at Nicklaus Children's Hospital.

Presurgical workup

Children with seizures were initially evaluated in the neurology clinic, where a detailed assessment of their seizure semiology, frequency, and age at seizure onset was performed. Developmental, past medical, surgical, and family histories were recorded, focusing on pertinent details of prematurity, history of infantile spasms, and central nervous system (CNS) insults (tumor, hemorrhage or hypoxia) and cortical malformation. Motor function, language competence, developmental milestones and visual fields were assessed.

EEG and VEEG monitoring captured waking and sleep interictal and ictal electrographic findings.

All patients underwent a comprehensive radiographic evaluation utilizing 3-Tesla magnetic resonance imaging (MRI). MRI diffusion tensor imaging (DTI) was occasionally used for tractography, and functional MRI (fMRI) was used to assess language dominance. Positron emission tomography (PET), ictal single-photon emission tomography (SPECT) and neuroelectromagnetic source imaging (NSI) were utilized selectively. Pertinent radiographic findings, including T2/FLAIR signal changes, polymicrogyria, focal cortical dysplasia, atrophy, infarction, and lesions, were noted. PET and SPECT findings of hypo- or hypermetabolic areas were also used to assess concordance with the seizure semiology and VEEG findings.

Nine children underwent formal pre-operative neuropsychological testing, which included assessment of overall intelligence, behavior, psychology and psychiatric co-morbidity. Intelligence was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI) or Wechsler Intelligence Scale for Children (WISC-IV) for patients aged $\geq$six years old, or the Wechsler Preschool and Primary Scale of Intelligence™ - Third Edition (WPPSI™ - III) for patients aged 3-7 years old.

Psychological screening was performed using two parental questionnaires, the Conner's Parent Report Scale-Revised (CPRS-R) and the Child Behavioral Checklist (CBCL). Academic achievement, school performance, and any learning disability was documented through clinical history taking. The Childhood Autism Rating Scale (CARS) was used to screen for pervasive development disorder. The Diagnostic and Statistical Manual of Mental Disorders (DSM IV) was used to assess psychiatric co-morbidity.

Children considered for surgery were presented at a weekly Epilepsy Surgery Case Conference. Based on seizure semiology, electrographic and MRI findings and functional imaging, a resective or disconnective procedure was proposed. Surgical intervention was offered to children who were unresponsive to AEDs and ancillary medications (benzodiazepines and corticosteroid therapy), and who evidenced neurocognitive decline coincident with ESES onset. In three cases, the children had decreased overall IQ scores and word processing speech on formal neuropsychological testing; in 10 cases, neurocognitive decline was reported by parents or documented academically through progressive academic delay. Children who met these criteria were assessed to be good surgical candidates, and underwent surgery at Nicklaus Children's Hospital by one of two neurosurgeons specialized in epilepsy.

Outcome

Post-operatively, children were re-evaluated by the neurology and neurosurgery services, and complications or unexpected deficits were recorded. Epilepsy outcome was assessed using the Engel classification at the time of last follow-up visit. Post-operative EEG or VEEG was performed to assess the degree of ESES resolution, and to evaluate interictal and ictal epileptiform activity during wakefulness. Postoperative neuropsychological outcome was obtained either through formal objective testing, or subjectively by parental questionnaires detailing the child's behavior, social interactions, verbal skills, and academic performance.

Results

Patient population

Of 9,502 pediatric patients who underwent VEEG evaluation at Nicklaus Children's Hospital between January 2009 and July 2016, 58 children met criteria for ESES. During the study period, 11 patients (19%) with an average age of 9.4 $\pm$ 3.4 years (range: 5-16 years) suffering from ESES underwent surgery at our institution (*table 2*).

Table 2. Preoperative information for children with ESES who later underwent surgical management.

Pt	Age (yr) Sex / Hand	Etiology	Age sz onset (yr)	Age ESES diagnosis	Seizure semiology	Seizure frequency	Neurologic deficit	Medications tried	Imaging	iiEEG asleep	iiEEG awake	Ictal EEG
1	12F / L	MCD	3	9	Focal to bilateral: R "tight face" sensation, oroalimentary automatisms, hypersalivation, clonic face/hand, aphasia, and secondary generalization	Daily	R hemiparesis	Active: CLB LEV LTG Tried: CBZ KD OXC TPM	MRI: L hemisphere insulo-opercular PMG PET: L opercular area hypermetabolism fMRI: L receptive, R expressive language	L ESES	L hemisphere nearly continuous posterior dominant rhythm with high-amplitude wave discharges	L fronto-central and insular focus
2	5M / R	MCD	2	4	Focal to bilateral: eyes turning to the L, decreased responsiveness and secondary generalization	Daily	L hemiparesis L VF deficit	Active: OXC Tried: VPA	MRI: microcephaly, R hemisphere PMG; thalamus atrophic NSI: R mesial temporal + R frontal convexity fMRI: L language	R > L ESES	R hemisphere slowing, frequent generalized spike-wave epileptiform activity	R posterior quadrant focus
3	10F / L	MCD	4.5	5.5	Focal to bilateral: dialeptic then clonic R hemibody motor convulsions with secondary generalization	Daily	R mild hemiparesis Language delay (LKS)	Active: VPA Tried: CBZ LEV LTG	MRI: L hemispheric FTP-insular PMG and L central FCD PET: concordant L hemisphere hypermetabolism NSI: R central L temporal fMRI: R language, BL vision	L ESES	L hemisphere slowing and spike-wave epileptiform activity, maximal in frontal-temporal region	L fronto-temporal focus

Table 2. Preoperative information for children with ESES who later underwent surgical management *(continued)*.

Pt	Age (yr) Sex / Hand	Etiology	Age sz onset (yr)	Age ESES diagnosis	Seizure semiology	Seizure frequency	Neurologic deficit	Medications tried	Imaging	iiEEG asleep	iiEEG awake	Ictal EEG
4	6F / R	Unknown; history of febrile seizure	3	4	Focal to bilateral: behavioral arrest, staring episodes, R arm clonic movements, with secondary generalization	Monthly	Non-verbal (LKS)	Active: CBZ OXC sulthiame	MRI: prior ATL with posterior margin gliosis and FCD PET: L posterior FTPi hypermetabolism NSI: L temporal (margin resection) fMRI: bilateral (L>R) language	L ESES	L fronto-parietal and centro-parietal epileptiform discharges	L posterior-temporal focus
5	16F / L	MCD	3	11.5	Focal non-motor: R arm sensory change that could spread to other extremities Focal to bilateral: behavioral arrest for 10-15 seconds with secondary generalization	Daily	R hemiparesis	Active: OXC ZNS	MRI: L hemisphere FTPi PMG sparing occipital lobe; thalamus normal PET: L hemisphere hypermetabolism, predominantly PTi NSI: L fronto-temporal lobes fMRI: BL vision	L ESES	L hemisphere continuous polymorphic slowing with multifocal spike discharges	L frontal focus
6	13F / L	Choroid plexus papilloma, IVH	3	10	Generalized motor	Monthly	R hemiparesis, fixed flexion deformity R VF deficit Nonverbal (LKS)	Active: LEV VPA Tried: LTG	MRI: L encephalomalacia involving thalamus, BL periventricular white matter changes iSPECT: Non-localizing	L > R ESES	R temporo-parietal and L frontal epileptiform discharges	R temporo-parietal and L frontal foci

Table 2. Preoperative information for children with ESES who later underwent surgical management *(continued)*.

Pt	Age (yr) Sex / Hand	Etiology	Age sz onset (yr)	Age ESES diagnosis	Seizure semiology	Seizure frequency	Neurologic deficit	Medications tried	Imaging	iiEEG asleep	iiEEG awake	Ictal EEG
7	7M / R	Unknown; history of electric injury	4	6	Focal to bilateral: L face and shoulder focal myoclonic twitches with secondary generalization Status epilepticus	Daily	L hemiparesis Moderate dysarthria (LKS)	Active: LTG Tried: CLB FPHT VPA OXC	MRI: L parietal DVA, mild L non-specific T2 hyperintensity iSPECT: R posterior fronto-parietal hyperperfusion fMRI: L language dominance	R ESES	R hemisphere diffuse slowing, maximal over R centro-parietal area	R frontal and paracentral focus
8	7F / R	Thalamic hemorrhage of unknown etiology	3	6	Generalized motor and non-motor Status epilepticus	Monthly	R mild hemiparesis Language delay (LKS)	Active: CLB LTG LEV Tried: VPA OXC PHT	MRI: L thalamic encephalomalacia with residual hemosiderin in L thalamus; L hippocampal sclerosis PET: L parietal hypermetabolic area	L ESES	L > R occipital generalized slowing and almost continuous epileptiform discharges	Not captured
9	10F / R	Rasmussen's encephalitis	6	8	Focal to bilateral: R sided tonic-clonic activity with twitching of face and eyes with secondary generalization	Weekly	Language delay (LKS)	Active: CLB perampanel Tried: LEV VPA ZNS	MRI: mild global atrophic changes, possible L hippocampal hyperintensity PET: L temporal hypometabolism, BL frontoparietal area hypometabolism	L ESES	L frontal operculum and insula epileptiform discharges	L temporal focus with propagation to the L, then R hemisphere

Table 2. Preoperative information for children with ESES who later underwent surgical management *(continued)*.

Pt	Age (yr) Sex / Hand	Etiology	Age sz onset (yr)	Age ESES diagnosis	Seizure semiology	Seizure frequency	Neurologic deficit	Medications tried	Imaging	iiEEG asleep	iiEEG awake	Ictal EEG
10	10F / L	Choroid plexus papilloma, IVH	0.5	7	Focal to bilateral: R eye deviation, R sided tonic-clonic activity with secondary generalization Status epilepticus	Monthly	R dense hemiparesis R VF deficit Language delay (LKS)	Active: Cannabidiol LEV Tried: CLB PHT VPA	MRI: L basal ganglia and hemisphere encephalomalacia and atrophy; ventriculomegaly PET: severe hypometabolism in the L lentiform nucleus, caudate body, frontal lobe, mesial anterior temporal lobe, and thalamus	L ESES	L temporal and anterior region intermittent slowing	Not captured
11	8F / L	L develop-mental poren-cephaly	6	7	Focal non-motor: R facial flushing, leg paresthesia	Daily	R hemiparesis and facial hemiparesis	Active: VPA Tried: CBZ PHT	MRI: L open lip schizencephaly and continuity with ventricular system	L ESES	L posterior quadrant continuous epileptiform activity	L epilepsia partialis continua

AED: anti-epileptic drug; ATL: anterior temporal lobectomy; BL: bilateral; CBZ: carbamazepine; CLB: clobazam; CPS: complex partial seizures; DTI: diffusion tensor imaging; ESES: epileptic status epilepticus during sleep; fMRI: functional magnetic resonance imaging; FPHT: fosphenytoin; ii: interictal; IVH: intraventricular hemorrhage; KD: ketogenic diet; L: left; LCM: lacosamide; LEV: levetiracetam; LKS: Landau-Kleffner syndrome; LTG: lamotrigine; MCD: malformation of cortical development; MRI: magnetic resonance imaging; N/A: not applicable; NSI: neuroelectromagnetic source imaging; OXC: oxcarbazepine; PET: positron emission tomography; PHT: phenytoin; PMG: polymicrogyria; pt: patient; R: right; SPECT: single-photon emission computed tomography; SPS: simple partial seizures; TPM: topiramate; VF: visual field; VNS: vagus nerve stimulator; VPA: valproic acid; yr: year; ZNS: zonisamide.

Mean age at seizure onset was 3.2 ± 1.9 years (range: 0.003-6 years) and the mean age at formal ESES diagnosis was 7.1 ± 2.4 years (range: 4-11.5 years). The most common etiology was cortical malformation (MCD), consisting of polymicrogyria (PMG) or focal cortical dysplasia (FCD) in four children. Three children had thalamic or intraventricular hemorrhage (IVH) and subsequent encephalomalacia; two as a result of surgery for choroid plexus papilloma, and one with unknown etiology. One child had Rasmussen's encephalitis and another had perinatal middle cerebral artery (MCA) infarct leading to developmental porencephaly. Two children had gliosis of unknown etiology. Two children experienced generalized seizures, including absence, atonic, and generalized convulsive semiologies; nine children experienced multiple focal seizure types. Secondary generalized seizures were the most common seizure semiology (eight patients), although one child experienced focal motor and non-motor seizures without generalization. Three patients experienced at least one documented episode of status epilepticus that required rescue medication and intensive care monitoring. Seizure frequency was daily (*n*=6), weekly (*n*=1), or monthly (*n*=4).

Preoperatively, nine children evidenced contralateral hemiparesis and three also had a homonymous hemianopsia. Seven children had language delay consistent with LKS. All patients were initially treated with AEDs and high-dose benzodiazepine (0.5-1.0 mg/kg diazepam at bedtime) as first-line therapy, followed by high-dose prednisone as second agent and administered over a period of one month. The ketogenic diet and vagus nerve stimulator (VNS) were also employed unsuccessfully in some patients. Five children were right-handed, and six were left-handed. Although handedness often correlated to ipsilateral ESES and contralateral paresis, three children had discordant handedness (Cases 4, 8, and 9).

Formal neuropsychological evaluation was performed at Nicklaus Children's Hospital on nine patients prior to surgery; the other children did not undergo formal evaluation due to either a language barrier or significant global delay (*table 3*). Neuropsychological impairments ranged widely, from global cognitive regression to more selective impairment of specific cognitive domains or expressive language. Overall intelligence was variable, with Intelligence Quotient (IQ) ranging from impaired to low average. Working memory index (WMI) and processing speed index (PSI) were impaired in the majority of children.

Pre-operatively, all patients had variable levels of developmental delay affecting different cognitive domains with documented regression. Furthermore, all patients experienced learning disability or poor academic performance. In addition, the majority of children displayed behavioral abnormalities, including impaired peer relations and social difficulties, aggression, hyperactivity, inattention, and emotional lability. Comorbidities included attention deficit hyperactivity disorder (ADHD), learning disorder, anxiety, and depression.

Radiography

MRI was performed for all children, and pertinent findings included hemispheric PMG, FCD, cerebral atrophy, focal sclerosis, and T2/FLAIR hyperintensity (*table 2*). Two patients had prior cerebral vascular insults. One child had hemispheric cystic encephalomalacia involving the thalamus (following prior tumor surgery and complicated by stroke) with additional contralateral white matter changes. Another patient had FCD and gliosis adjacent to a prior anterior temporal lobectomy (ATL) resection cavity. The child with prior MCA stroke had a large developmental porencephalic lesion and open-lip schizencephaly. In order to document thalamic involvement in ESES (Guzzetta *et al*., 2005), particular attention was paid to the appearance of the ipsilateral thalamus on radiography. Five children displayed thalamic changes on MRI (encephalomalacia, T2/FLAIR signal changes, and atrophy).

All children underwent either PET or SPECT, which revealed areas of hypo- or hyper-metabolism/perfusion concordant with the EEG findings, and provided additional lateralizing confirmation to support operative management.

Neurophysiology

All patients underwent VEEG monitoring preoperatively, with hemi-ESES isolated to the left hemisphere in eight children and right hemisphere in one child (*table 2*). Two children had bilateral ESES suggesting two-way (Pertola Type III) interhemispheric propagation. Electroclinical seizures during wakefulness were captured on VEEG in nine patients, showing epileptiform discharges from abnormal cerebral foci that were concordant with radiographic findings. In all cases, the ictal epileptic focus during wakefulness was located in the same hemisphere as the ESES electrographic findings.

Surgery

In this cohort, seven children underwent focal cortectomy and resection, and four children underwent hemispherectomy and disconnection (*table 4*). Surgery was undertaken in children following documentation of cognitive performance based on serial neuropsychological tests and deterioration in school performance. The period of time necessary to

Table 3. Preoperative neuropsychological evaluation assessing intelligence, academic capability, and behavioral / psychological impairment.

Pt	Age at last assessment (yrs)	Intelligence* (WASI, WPPSI or WSIC 4)			Documented deterioration over time	Academic	Behavioral / psychological impairment			
		FSIQ / VIQ / PIQ	WMI	PSI			Hyperactive	Conduct	Social / peer	Comorbidities
1	12	87 / 87 / 88	80	75	Yes (inattention, executive functioning)	Grade 6	No	Aggression, inattention, poor executive functioning	Impaired	Learning disability, anxiety
2	4.5	57 / 61 / 53	N/A	50	Yes (global)	Pre-academic skills delayed (Bracken-R)	Yes	Aggressive, low frustration tolerance, temper tantrums	Impaired	ADHD
3	10	78 / 89 / 72	77	80	Yes (verbal memory)	Grade 3 (delayed)	No	Moodiness, inattention	Social withdrawal	Learning disability, ADHD
4	Not performed – significant language barrier						No	None	Impaired	Severe global delay
5	11.5	82 / 92 / 75	74	78	Yes (behavioral issues only)	Grade 3 (delayed)	No	Aggression	Impaired	Depression, anxiety
6	Not performed – significant global delay						No	None	Impaired	Severe global delay
7	6.5	79 / 77 / 86	90	65	N/A	N/A	Yes	Inattention, poor concentration and memory / organizational skills, impulsivity	Impaired	Vocal tics, speech problems
8	6	62 / 61 / 65	94	62	Yes (previously normal)	Kindergarten (delayed)	No	None	None	None
9	6	79 / 77 / 88	N/A	75	N/A	Grade 1	Yes	Inattention, poor executive functioning and mood	Impaired	Learning disability, ADHD, depression
10	8	56 / 79 / 45	68	68	Yes (non-verbal memory, conceptual reasoning and math)	Grade 2 (delayed)	No	None	None	None
11	7	78 / 81 / 79	59	78	Yes (global)	Grade 1 (delayed)	Yes	Inattention, uncooperative, poor focus, irritability	Impaired	ADHD, anxiety

ADHD: attention deficit hyperactivity disorder; FSIQ: full scale intelligence quotient; IQ: intelligence quotient; N/A: not applicable; pt: patient; PIQ: performance intelligence quotient; PSI: processing speed index; VIQ: visual intelligence quotient; WASI: Wechsler Abbreviated Scale of Intelligence; WMI: working memory index; WPPSI: Wechsler Preschool and Primary School of Intelligence; WSIC 4: Wisconsin Statewide Intelligence Center, version 4; yrs: years.
*90-100: average; 80-89: low-average; 70-79: borderline; ≤69: extremely low.

Table 4. Procedure, pathology, and post-operative outcome (seizure, neuropsychological, and electrographic) in patients undergoing surgery for ESES.

Pt	Surgery	Pathology	F/U (months)	AED last F/U	Seizure outcome (Engel)	Neuropsychological outcome	Postop iiEEG
1	L perisylvian fronto-temporo-parietal opercular resection	FCD Ic	70	LEV, LTG	II	Improvement: significant improvement in verbal skills and working memory. Better cognition and sleep; good school and academic performance.	Resolution of ESES; normal EEG.
2	R functional hemispherectomy	FCD Ia PMG Chaslin's gliosis	28	LEV, OXC	III	No improvement: persistent deficits in overall intellectual and cognitive functioning.	Persistent ESES in R hemisphere; slowing with nearly continuous epileptiform discharges over R frontal and temporal regions.
3	L posterior Rolandic parieto-temporal cortectomy (following implantation)	PMG	56	LEV	I	Improvement: better learning, academic performance, attention / focus, mood, independence, and memory. Persistent difficulty with arithmetic and logic analysis.	Resolution of ESES; persistent independent R frontal predominant and L temporal epileptiform discharges representing underlying cortical irritability with lowered seizure threshold.
4	2 surgeries: L anterior temporal lobectomy, followed by L superior temporal gyrus cortectomy	FCD 1c Chaslin's gliosis	36	Sulthiame	II	Improvement: better social skills and behavior, starting to trace words and sounds letters, but still unable to read	Persistent ESES with L fronto-temporal discharges.
5	L functional hemispherectomy	FCD Ib PMG Chaslin's gliosis	54	OXC	I	Improvement: better verbal expression and communication, cognition, and independence. Achieving A and B in school, special classes. Improved mood and anxiety.	Resolution of ESES; persistent L hemisphere continuous polymorphic slowing, multifocal spike discharges.

Table 4. Procedure, pathology, and post-operative outcome (seizure, neuropsychological, and electrographic) in patients undergoing surgery for ESES. *(continued)*.

Pt	Surgery	Pathology	F/U (months)	AED last F/U	Seizure outcome (Engel)	Neuropsychological outcome	Postop iiEEG
6	2 surgeries: L functional hemispherectomy, followed by anatomical hemispherectomy	FCD Ia Chaslin's gliosis	60	CLB, VPA	IV	No improvement: significant global delay and dependent.	N/A
7	R inferior fronto-parietal cortectomy	FCD Ib	100	None	II	Improvement: doing well socially and academically in school with no learning issues	Resolution of ESES; normal EEG.
8	L parietal cortectomy	Gliosis	30	CLB, hemp oil	II	No improvement: speech remains slow and halting, lacking in prosody.	Resolution of ESES; persistent frequent epileptiform discharges in L hemisphere during sleep, less relative to prior studies.
9	L posterior frontal cortectomy	Gliosis	27	CLB Perampanel	III	Improvement: better sleep and behavior.	Resolution of ESES; persistent L fronto-temporal slowing, parietal epileptiform discharges.
10	L parietal cortectomy (ECoG guided)	Cortical gliosis and acute hypoxic change	25	None	I	Improvement: better conversation skills, social skills, memory, comprehension. More independent with daily activities. Improved drawing, reading, and academic work.	Resolution of ESES; persistent L frontotemporal slowing.
11	L functional hemispherectomy (endoscopic posterior parieto-occipital disconnection)	N/A	24	None	I	Improvement: better cognition, learning, and academic performance. Persistent problems with behavior and mood.	Resolution of ESES; persistent L hemisphere background slowing.

AED: antiepileptic drug; ATL: anterior temporal lobectomy; BL: bilateral; CLB: clobazam; ECoG: electrocorticography; EEG: electroencephalogram; FCD: focal cortical dysplasia; F/U: follow-up; FPT: fronto-parieto-temporal; ii: interictal; L: left; LEV: levetiracetam; N/A: not applicable; PMG: polymicrogyria; pt: patient; R: right; VPA: valproic acid.

confirm these parameters was variable, but was never less than a year from the diagnosis of ESES. Children who responded to a period of conservative medical management with diazepam, prednisone and AEDs continued to be managed medically and followed in our Comprehensive Epilepsy Program.

Focal cortectomies were performed for children with VEEG and MRI findings that supported a localized epileptogenic focus, accompanied by a consistent seizure semiology and history. In some cases, operative adjuncts including subdural grid electrodes and intra-operative electrocorticography (ECoG) were used to guide the extent of resection. One child with left fronto-temporo-parietal and insular PMG, left hemisphere ESES, and a left temporo-parietal epileptic focus underwent subdural grid insertion followed by focal resection (Case 3). Another child with left ESES and MRI findings of basal ganglia and hemispheric signal abnormality, underwent ECoG-guided resection to achieve a maximally safe resection (Case 10).

Four children underwent functional peri-Sylvian hemispherectomies, one of whom required a subsequent anatomical hemispherectomy for persistent seizures (Case 6). This child had significant global delay due to daily seizures, and underwent surgical disconnection of multiple areas of neurologic injury and bilateral encephalomalacia, with a VEEG that revealed bilateral ESES and bilateral epileptogenic foci. Unfortunately, she experienced no seizure relief following the functional-, and later anatomical- hemispherectomies. Another patient with left hemispheric PMG and thalamic atrophy and hemispheric slowing and spike-wave discharges also underwent functional hemispherectomy (Case 2). A third patient underwent hemispherectomy for a large area of fronto-temporo-parietal PMG with multi-focal epileptiform discharges (Case 5). Lastly, a patient with left-sided developmental porencephaly underwent endoscopic disconnection of the posterior quadrant, essentially equivalent to a functional hemispherectomy (Case 11).

Pathological tissue analysis was unavailable for the patient undergoing endoscopic disconnection; abnormal pathological findings were observed in 10 specimens including FCD or PMG (n=7) and gliosis (n=3).

Clinical and neurophysiological outcome

There were no procedure-related complications, and all patients were discharged within a few days of surgery. Nine children experienced improvement in seizure frequency, and four children had complete seizure freedom (Engel Class I) at the time of the most recent follow-up visit.

Children with extensive cerebral injury and bilateral ESES activity pre-operatively experienced little or no seizure improvement (Engel Class III and IV). One child (Case 2) became seizure-free after a right hemispherectomy, but subsequently developed seizure recurrence 14 months post-operatively. Investigation with ictal SPECT revealed increased perfusion in the right basal ganglia and thalamus, and VEEG revealed nearly continuous independent epileptiform discharges in the right frontal and temporal regions. Another child with epilepsy due to an extensive CNS insult from choroid plexus papilloma and hemorrhage had no improvement at the last follow-up visit (Case 6). Unfortunately, she continued to experience intractable epilepsy despite extensive medical and surgical treatment. She was not assessed with post-operative VEEG.

Parents reported subjective neurocognitive, academic, social, and behavioral improvement in eight children, although all exhibited selective persistent deficits (*table 4*). Improved academic performance and learning included higher school achievement and improved cognition, processing speed, memory, verbal skills, and reading. Some children were able to return to regular school with good academic performance. Social and behavioral improvement included better interactions with family and schoolmates, increased social insight, and greater independence. Improved behavior and mood, including amelioration of anxiety and depressive symptoms, were also noted. Three children had significant developmental delay at baseline and subsequently did not experience neuropsychological improvement.

Ten patients underwent post-operative EEG or VEEG (*table 4*). Of those, two had persistent ESES and six had resolution of ESES with some persistent abnormal electrographic activity. Notably, two children had post-operative normal EEGs with no evidence of ictal or interictal abnormalities in either the waking or sleep states (Case 7 and 10). The resolution of VEEG findings was concordant with improved seizure and neurocognitive outcomes. One child (Case 7) improved significantly in both social and academic domains; he was more engaging with friends, learned new material faster, and displayed improved focus and attention. He had only occasional seizures. The other child (Case 10) had complete resolution of seizures and improved neurocognitive outcomes. Post-operatively, she was able to resume normal activities, return to regular school, travel, and exhibited improved mood and behavior. Both children with normal EEGs were weaned off their AEDs completely.

Discussion

ESES is an age-dependent disorder associated with epilepsy, cognitive decline and behavioral impairment.

It is a relatively new entity, first described in 1971 in six children with continuous spike-wave discharges during non-REM sleep that subsided on awakening. The clinical presentation of children with ESES is variable, ranging from early-onset developmental delay to global cognitive regression with clinical seizures (van den Munckhof *et al*., 2015). The average age at ESES diagnosis is 6.9 years (range: 1-11.5 years), and most present with seizures, although it is absent in 20% of cases (van den Munckhof *et al*., 2015). The average age at ESES diagnosis in our cohort (7.1 years) is consistent with published studies, although our surgical series contains a disproportionate number of children with symptomatic seizures and neurocognitive decline.

As a relatively new entity, the pathophysiology and natural history of ESES is poorly understood. The occurrence of *GRIN2A* mutations in familial cases (Carvill *et al*., 2013; Lemke *et al*., 2013; Lesca *et al*., 2013; Lesca *et al.,* 2019), underlying inflammatory disorders, or prior cerebral insults have been postulated as potential etiologies. However, the etiology was unknown in almost half of patients in a recent meta-analysis of 575 cases (van den Munckhof *et al*., 2015). Early recognition and effective therapy are crucial to improving the long-term neurocognitive prognosis. The natural history of ESES is thought to be a self-limiting condition, usually ceasing around puberty. However, long-term neuropsychological sequelae often remain, with permanent cognitive impairments estimated at 40%-60% (Kramer *et al*., 2009; Liukkonen *et al*., 2010a). Therefore, the major goal of ESES treatment is to resolve seizures and halt neurocognitive decline.

Medical therapy improves or abolishes ESES in only half of patients (Veggiotti *et al*., 2012). Furthermore, most symptomatic ESES non-responders to medical therapy develop cognitive decline (Caraballo *et al*., 2013) and less than half regain baseline cognitive status (Guerrini *et al*., 1998; Liukkonen *et al*., 2010b; Veggiotti *et al*., 2001, 2012; Smith and Hoeppner, 2003). Although neuropsychological and seizure outcomes respond to medical therapy in many cases, surgery remains an important option, especially for children with ESES secondary to a structural lesion. Specifically, based on the recent meta-analysis, surgery led to neurocognitive and epilepsy improvement in 80% of cases, exceeding the benefit of AEDs, benzodiazepines, and steroids (van den Munckhof *et al*., 2015). We acknowledge, however, that our cohort is still small and that our findings await confirmation from additional studies with larger samples.

Although other authors have reported small case series with resective procedures, or larger series with MST for children with LKS (*table 1*), to our knowledge, this is the largest case series with resective and disconnective surgical management for ESES reported to date. Heterogeneous pathologies including PMG, FCD, hypoxia, and hemorrhage were represented in our cases. All seven children who underwent focal cortical resections for hemi-ESES improved postoperatively. Their favorable outcomes are consistent with the hypothesis that their declines were secondary to epileptic encephalopathy and pathology-independent. Thus, similar to other patients with a focal seizure etiology, localized excision of the seizure-onset zone in children with ESES is also beneficial.

A less favorable outcome in two of the four children who underwent hemispherectomies was related to incomplete resection of the epileptogenic zone. Both patients evidenced bilateral ESES pre-operatively, and persistent electrographic ESES post-operatively. One patient made no recovery (Engel Class IV), while the other had minor improvement in seizure frequency (Engel Class III). There were no neuropsychological, behavioral or intellectual improvements in either child. Of note, the presence of bilateral ESES likely heralds a poorer epileptic prognosis when bilateral ESES is asynchronous with bi-directional interhemispheric propagation (Peltola type 3 pattern), suggesting incomplete removal of ESES-generating cortex with uni-hemispheric surgery.

Early surgical intervention, especially in medical non-responders, can halt cognitive decline and abolish epileptic EEG patterns. We noted similar results as cognitive regression was halted in the majority of our patients and gains were obtained in a small subset (*table 4*). However, some degree of cognitive and behavioral impairment persisted in all patients, suggesting that surgery cannot fully reverse pre-existing cognitive deficits. A similar outcome has been reported for conventional paediatric epilepsy surgery for other epileptic encephalopathies (Roulet-Perez *et al*., 2010).

Bartolini *et al* reported on a cohort of 27 patients with ESES in polymicrogyric cortex and noted that complete remission occurred by age 13 years (Bartolini *et al*., 2016). This long-term study confirmed that the natural evolution of ESES involves spontaneous remission in patients with this etiology. While this outcome might favor medical rather than surgical treatment, this cohort ultimately evidenced variable degrees of cognitive disability. It therefore remains unclear whether earlier surgical intervention might have prevented some of the permanent cognitive sequelae.

In this small case series of 11 children who underwent surgery for ESES, resection or disconnection improved seizure control and neuropsychological outcome in most patients. However, children with non-resected or bilateral ESES have persistent seizures and neuropsychological impairment. In ESES, the aim

of treatment is to control both clinical seizures and paroxysmal EEG abnormalities, in order to improve motor, language, and cognitive functions. Although our cohort is too small to identify statistically significant risk factors, reduced epileptic and neurocognitive improvement occurred in patients who were more severely cognitively impaired and exhibited incompletely resected or bilateral epileptogenic and ESES foci, and non-resolution of postoperative ESES. Although the numbers are too small to be conclusive, these findings are reported in prior surgical series (*table 1*). Improved post-operative cognitive status is uncommon, and typically occurs in children with less severe developmental delay, preoperative IQ >75, and shorter time to treatment.

Although ESES is a relatively new entity with poorly understood etiology and natural history, increasing evidence advocates for early recognition and aggressive management. It would be reasonable to consider a six to 12-month course of escalating medical treatment, involving AEDs initially, and advancing to benzodiazepines, corticosteroids, and IVIG. If the child continues to experience persistent seizures or neuropsychological decline, surgical management in the form of resection or disconnection should be considered. As seen in this series and the recent literature, surgery is most favorable for developmentally normal children with early documented neuropsychological regression and be considered for patients with known ESES etiology, hemi-ESES findings, and focal epileptogenic focus and radiographic findings. Additional research on the optimal timing of surgery and the factors associated with improved outcome would be beneficial for the management of children with this new and rare entity. □

Disclosures.
None of the authors have any conflict of interest to declare.

References

Aeby A, Poznanski N, Verheulpen D, Wetzburger C, Van Bogaert P. Levetiracetam efficacy in epileptic syndromes with continuous spikes and waves during slow sleep: experience in 12 cases. *Epilepsia* 2005; 46: 1937-42.

Arzimanoglou A, Cross HJ. Cognitive impairment and behavioral disorders in Encephalopathy related to Status Epilepticus during slow Sleep: diagnostic assessment and outcome. *Epileptic Disord* 2019; 21(S1): 71-5.

Bahi-Buisson N, Savini R, Eisermann M, *et al*. Misleading effects of clonazepam in symptomatic electrical status epilepticus during sleep syndrome. *Pediatr Neurol* 2006; 34(2): 146-50.

Bartolini E, Falchi M, Zellini F, *et al*. The syndrome of polymicrogyria, thalamic hypoplasia, and epilepsy with CSWS. *Neurology* 2016; 86: 1250-9.

Battaglia D, Veggiotti P, Lettori D, *et al*. Functional hemispherectomy in children with epilepsy and CSWS due to unilateral early brain injury including thalamus: sudden recovery of CSWS. *Epilepsy Res* 2009; 87(2-3): 290-8. Erratum in: *Epilepsy Res* 2010; 89(2-3): 365.

Caraballo R, Vaccarezza M, Cersosimo R, *et al*. Long-term follow-up of the ketogenic diet for refractory epilepsy: multicenter Argentinean experience in 216 pediatric patients. *Seizure* 2011; 20: 640-5.

Caraballo RH, Fortini S, Cersosimo R, *et al*. Rasmussen syndrome: an Argentinean experience in 32 patients. *Seizure* 2013; 22: 360-7.

Carvill GL, Regan BM, Yendle SC, *et al*. *GRIN2A* mutations cause epilepsy-aphasia spectrum disorders. *Nat Genet* 2013; 45: 1073-6.

Fejerman N, Caraballo R, Cersosimo R, Ferraro SM, Galicchio S, Amartino H. Sulthiame add-on therapy in children with focal epilepsies associated with encephalopathy related to electrical status epilepticus during slow sleep (ESES). *Epilepsia* 2012; 53: 1156-61.

Galanopoulou AS, Bojko A, Lado F, Moshe SL. The spectrum of neuropsychiatric abnormalities associated with electrical status epilepticus in sleep. *Brain Dev* 2000; 22: 279-95.

Guerrini R, Genton P, Bureau M, *et al*. Multilobar polymicrogyria, intractable drop attack seizures, and sleep-related electrical status epilepticus. *Neurology* 1998; 51: 504-12.

Guzzetta F, Battaglia D, Veredice C, *et al*. Early thalamic injury associated with epilepsy and continuous spike-wave during slow sleep. *Epilepsia* 2005; 46: 889-900.

Jansen FE, Nikanorova M, Peltola M. Current treatment options for Encephalopathy related to Status Epilepticus during slow Sleep. *Epileptic Disord* 2019; 21(S1): 76-81.

Jeong A, Strahle J, Vellimana AK, Limbrick Jr. DD, Smyth MD, Bertrand M. Hemispherotomy in children with electrical status epilepticus of sleep. *J Neurosurg Pediatr* 2017; 19(1): 56-62.

Kallay C, Mayor-Dubois C, Maeder-Ingvar M, *et al*. Reversible acquired epileptic frontal syndrome and CSWS suppression in a child with congenital hemiparesis treated by hemispherotomy. *Eur J Paediatr Neurol* 2009; 13(5): 430-8.

Kramer U, Sagi L, Goldberg-Stern H, Zelnik N, Nissenkorn A, Ben-Zeev B. Clinical spectrum and medical treatment of children with electrical status epilepticus in sleep (ESES). *Epilepsia* 2009; 50: 1517-24.

Lemke JR, Lal D, Reinthaler EM, *et al*. Mutations in *GRIN2A* cause idiopathic focal epilepsy with rolandic spikes. *Nat Genet* 2013; 45: 1067-72.

Lesca G, Rudolf G, Bruneau 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.

Lesca G, Møller RS, Rudolf G, Hirsch E, Hjalgrim H, Szepetowski P. Update on the genetics of the epilepsy-aphasia spectrum and role of *GRIN2A* mutations. *Epileptic Disord* 2019; 21(S1): 41-7.

Liukkonen E, Kantola-Sorsa E, Paetau R, Gaily E, Peltola M, Granström M-L. Long-term outcome of 32 children with encephalopathy with status epilepticus during sleep, or ESES syndrome. *Epilepsia* 2010a; 51: 2023-32.

Liukkonen E, Kantola-Sorsa E, Paetau R, Gaily E, Peltola M, Granstrom ML. Long-term outcome of 32 children with encephalopathy with status epilepticus during sleep, or ESES syndrome. *Epilepsia* 2010b; 51: 2023-32.

Loddenkemper T, Cosmo G, Kotagal P, *et al*. Epilepsy surgery in children with electrical status epilepticus in sleep. *Neurosurgery* 2009; 64(2): 328-37.

Nass R, Heier L, Walker R. Landau-Kleffner syndrome: temporal lobe tumor resection results in good outcome. *Pediatr Neurol* 1993; 9(4): 303-5.

Pal DK, Ferrie C, Addis L, Akiyama T, Capovilla G, Caraballo R, de Saint-Martin A, Fejerman N, Guerrini R, Hamandi K, Helbig I, Ioannides AA, Kobayashi K, Lal D, Lesca G, Muhle H, Neubauer BA, Pisano T, Rudolf G, Seegmuller C, Shibata T, Smith A, Striano P, Strug LJ, Szepetowski P, Valeta T, Yoshinaga H, Koutroumanidis M. Idiopathic focal epilepsies: the "lost tribe". *Epileptic Disord* 2016; 18(3): 252-88.

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.

Peltola ME, Liukkonen E, Granström ML, *et al*. The effect of surgery in encephalopathy with electrical status epilepticus during sleep. *Epilepsia* 2011; 52(3): 602-9.

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.

Roulet Perez E, Seeck M, Mayer E, Despland PA, de Tribolet N, Deonna T. Childhood epilepsy with neuropsychological regression and continuous spike waves during sleep: epilepsy surgery in a young adult. *Eur J Paediatr Neurol* 1998; 2(6): 303-11.

Roulet-Perez E, Davidoff V, Mayor-Dubois C, *et al*. Impact of severe epilepsy on development: recovery potential after successful early epilepsy surgery. *Epilepsia* 2010; 51: 1266-76.

Rubboli G, Tassinari CA. Encephalopathy related to Status Epilepticus during slow Sleep: an historical introduction. *Epileptic Disord* 2019; 21(S1): 3-4.

Sawhney IM, Robertson IJ, Polkey CE, Binnie CD, Elwes RD. Multiple subpial transection: a review of 21 cases. *J Neurol Neurosurg Psychiatry* 1995; 58(3): 344-9.

Smith MC, Hoeppner TJ. Epileptic encephalopathy of late childhood: Landau-Kleffner syndrome and the syndrome of continuous spikes and waves during slow-wave sleep. *J Clin Neurophysiol* 2003; 20: 462-72.

Tassinari CA, Rubboli G. Encephalopathy related to Status Epilepticus during slow Sleep: current concepts and future directions. *Epileptic Disord* 2019; 21(S1): 82-7.

Tassinari CA, Rubboli G, Volpi L, *et al*. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. *Clinical Neurophysiol* 2000; 111(2): S94-102.

van den Munckhof B, van Dee V, Sagi L, *et al*. Treatment of electrical status epilepticus in sleep: a pooled analysis of 575 cases. *Epilepsia* 2015; 56: 1738-46.

Veggiotti P, Bova S, Granocchio E, Papalia G, Termine C, Lanzi G. Acquired epileptic frontal syndrome as long-term outcome in two children with CSWS. *Neurophysiol Clin* 2001; 31: 387-97.

Veggiotti P, Pera MC, Teutonico F, Brazzo D, Balottin U, Tassinari CA. Therapy of encephalopathy with status epilepticus during sleep (ESES/CSWS syndrome): an update. *Epileptic Disord* 2012; 14: 1-11.

Vigliano P, Margary G, Bagnasco I, Jarre L. Cognitive evolution of a girl submitted to right hemispherotomy when five years old. *Brain Dev* 2010; 32(7): 579-82.

TEST YOURSELF

(1) What is ESES, and what is its clinical relevance in epilepsy and neuropsychology?

(2) What are potential treatment options for ESES?

(3) In children who undergo resective or disconnective surgery for ESES, what are the clinical variables leading to favorable post-operative outcome?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".