

Co-morbidities of Pediatric Epilepsy

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Cerebral Palsy

Cerebral Palsy (CP)

- Injury to a developing brain (before 3 years)
- Motor system affected
- Not progressive

Seizures more
likely to occur



Common Causes of CP

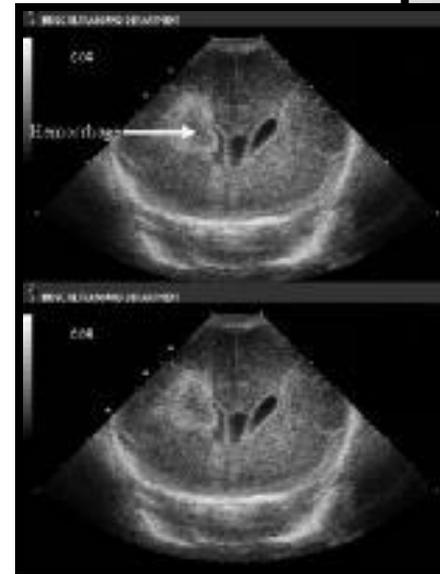
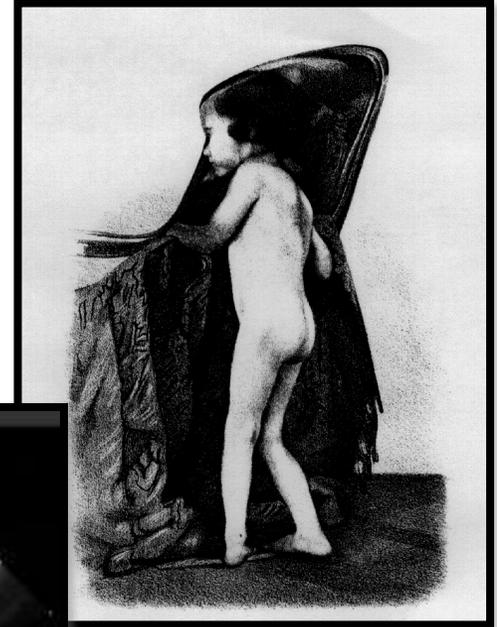
1. Intraventricular hemorrhage
2. Congenital stroke
3. Periventricular leukomalacia
4. Other
 - Trauma
 - Infection
 - Congenital malformations
 - Toxin exposures....



Intraventricular Hemorrhage



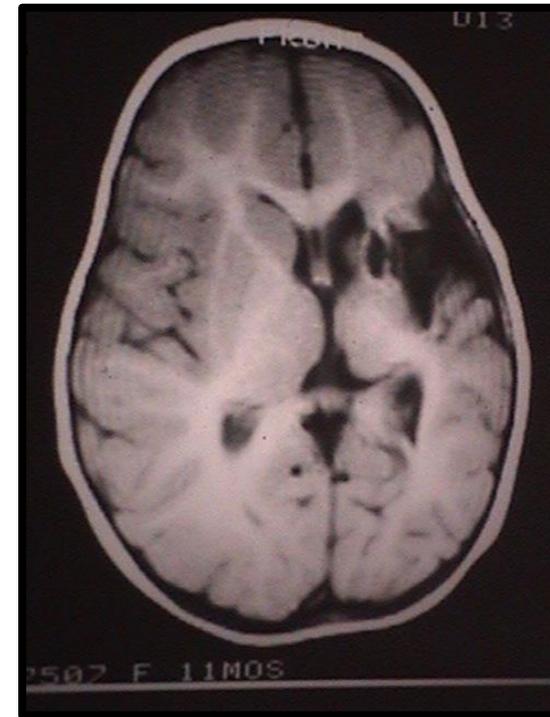
- Perinatal germinal matrix bleeding
- Grade 1-4
 - Germinal matrix
 - Intraventricular
 - Intraventricular with hydrocephalus
 - Intraparenchymal



Congenital Stroke

- **Neonatal presentation**
 - Seizures, lethargy, jittery
 - Often normal
- **Hemiparesis**
 - Develops over time
 - Early hand preference (6 to 12 months)
- **Often MCA (middle cerebral artery)**
 - 75% on left
 - Face, arm, language cortex
 - Normal language by school! (neuroplasticity)

Focal Lesion – Focal
Seizures Focal Drugs



Periventricular Leukomalacia

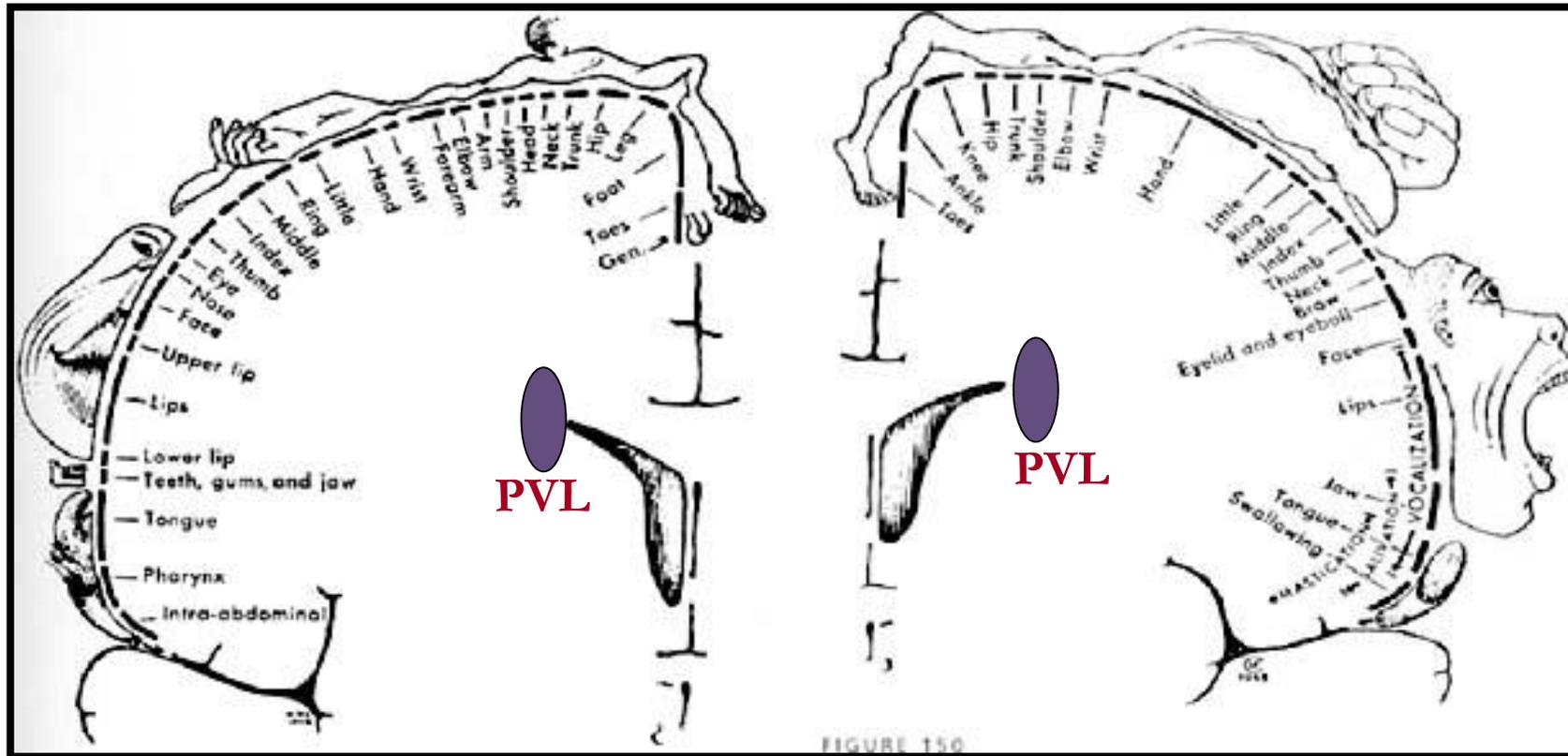
- ~24-34 weeks gestation
- Periventricular white matter selectively vulnerable
- Gliosis
- Outcome: spastic diplegia
- Most common form of CP



Periventricular Leukomalacia

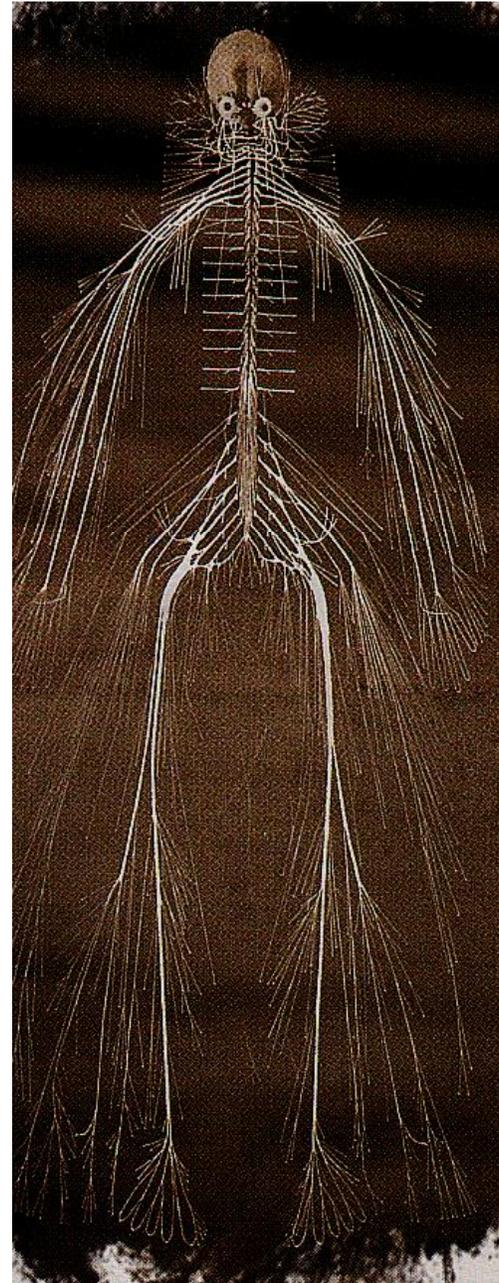
(affects legs > arms)

(leg corticospinal tracts loop closer to ventricles than arm tracts)



Spasticity- Why?

- Interference with central inhibition
- Impaired spinal regulation of α -motor neuron



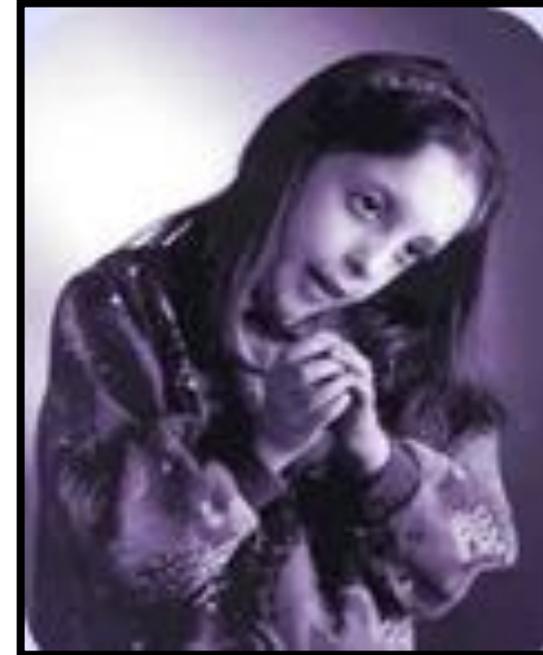
Diagnosing CP

- Delayed motor milestones
- Abnormalities of tone
 - Spasticity
 - Chorea
 - Dystonia
- Early hand dominance
- Persistence of neonatal reflexes



CP-What It Isn't

- Progressive spasticity
- Degenerating cognitive disorder
- Normal motor system
 - By definition is a motor *abnormality*
- Acquired after early childhood
 - Can be a neurodevelopmental disability, not CP



Classification

Motor Abnormality

Spastic

Dystonic/Choreoathetotic

Hypotonic

Ataxic

Location

Diplegic

Hemiplegic

Quadriplegic

Monoplegic



Treatment

- Set Goals
 - Realistic
 - Meaningful
 - Measurable
- Formulate Plan
 - Tone reduction?
 - Bracing?
 - Intensive therapy?
- Reassess
 - Goals met?
 - Need readjustment?



Spasticity- Good & Bad

Spasticity = Good	Spasticity = Bad
Aids standing and walking	Impaired standing
Maintenance of muscle mass	Impaired swing phase of gait
Helps preserve skeletal mass	Slow voluntary movements
Decreases dependent edema	Skin shear
Reduced risk of DVT	Risk contractures/joint subluxation
	Pain
	Insomnia
	More difficult hygiene



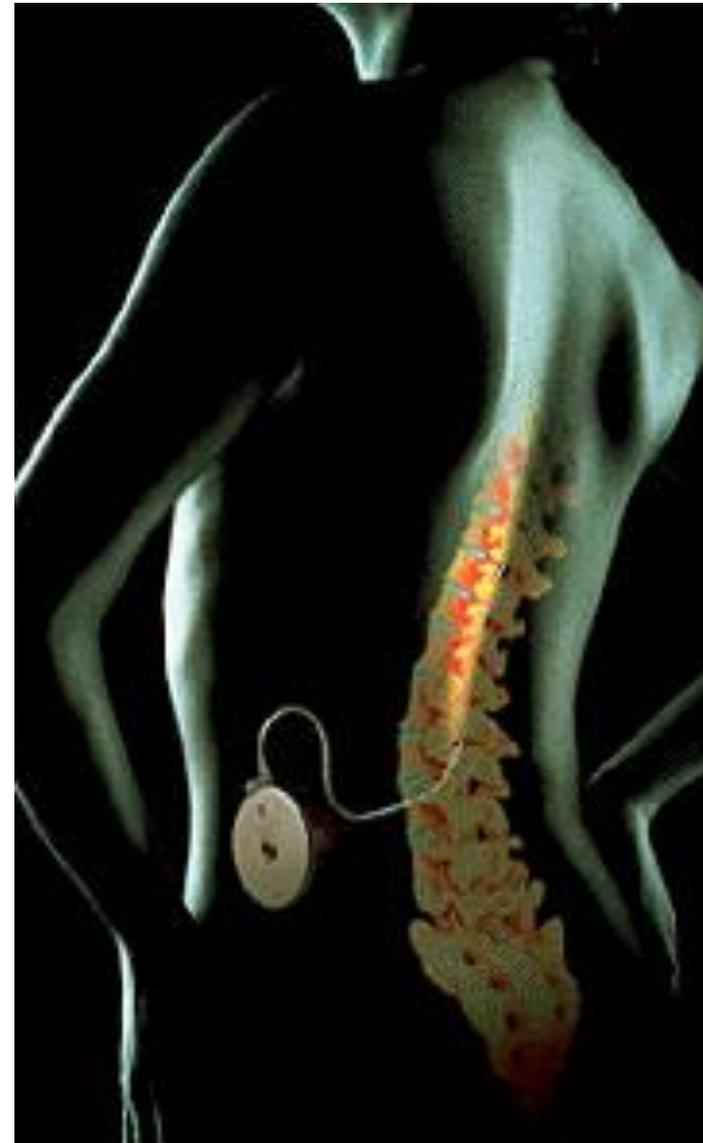
Spasticity Treatment-*Medications*

Primary Drugs	Secondary Drugs
Diazepam	Tiagabine
Baclofen	Cyproheptadine
Dantrolene	Clonidine
Tizanidine	Lamotrigine
	Gabapentin
	Maybe also: thorazine, madafinil, THC..



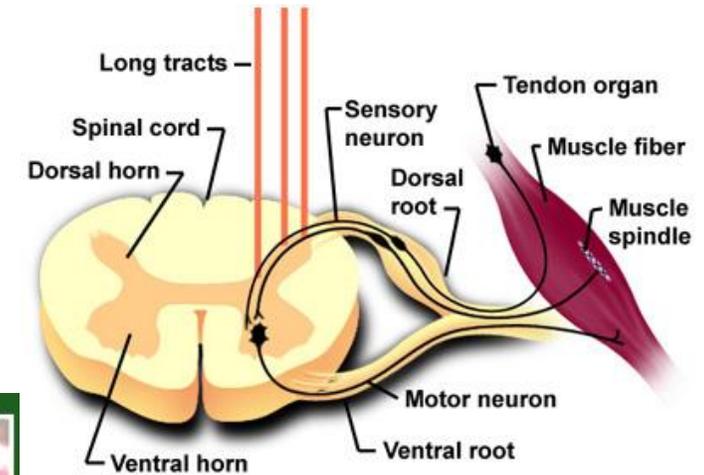


Baclofen Pump



Selective Dorsal Rhizotomy

- Permanent
- Unmasks
 - Underlying
 - Weakness
- Aggressive therapy
 - Post op



Other Spasticity Options

Treatment options

- Home stretching
- Braces
- Oral medication
- Neurolysis
 - Phenol
- Chemical denervation
 - Botulinum toxin
- Baclofen pump
- Selective dorsal rhizotomy
- Orthopedic surgery



Serial Casting



SUDDEN UNEXPECTED DEATH IN EPILEPSY

ARTICLE IN PRESS

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Topical Review

Pediatric Sudden Unexpected Death in Epilepsy

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Classification of SUDEP

TABLE 1.

Proposed Unified Sudden Unexpected Death in Epilepsy (SUDEP) Definition and Classification¹⁰

Proposed Unified SUDEP Definition and Classification

1. Definite SUDEP*:

Sudden, unexpected, witnessed, or unwitnessed, nontraumatic and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration > or = 30 minutes or seizures without recovery in between), in which postmortem examination does not reveal a cause of death

1a. Definite SUDEP Plus*:

Satisfying the definition of Definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the death may have been due to the combined effect of both conditions, and if autopsy or direct observations/recordings of terminal event did not prove the concomitant condition to be the cause of death

2. Probable SUDEP/Probable SUDEP Plus*:

Same as Definite SUDEP but without autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death

3. Possible SUDEP*:

A competing cause of death is present

4. Near-SUDEP/Near-SUDEP Plus:

A patient with epilepsy survives resuscitation for more than 1 hour after a cardiorespiratory arrest that has no structural cause identified after investigation

5. Not SUDEP: A clear cause of death is known

6. Unclassified: Incomplete information available; not possible to classify

* If a death is witnessed, an arbitrary cutoff of death within 1 hour from acute collapse is suggested.

Epidemiology of SUDEP in the USA

- SUDEP in USA per year: 3,000 to 5,000 in adults
- Risk of SUDEP much less in children, varying between 1.1 and 3.4 per 10,000 patient-years (Morse, 2016)
- 0.5-1% of the epilepsy population with drug resistant symptomatic epilepsy dies of sudden death with no apparent explanation
- In patients with chronic refractory epilepsy who attend epilepsy referral centers, SUDEP is the leading cause of premature death



What are the Risk Factors for Sudep?

- 1.4 times higher in males than females (> for males) - *Walczak et al Neurology 2001*
- 1.72 times higher if onset before age 16 than 16 to 60.
- 1.95 times higher if epilepsy > 15 years
- Odds ratios for generalized tonic-clonic seizures per year:
 - 2.94 1-2
 - 8.28 3-12
 - 9.06 13-50
 - 14.51 >50
- Odds ratio for polytherapy:
 - 1.95



Unexpected SUDEP

SUDEP can occur:

- At any age
- In patients with infrequent seizures
- With a first seizure after a long period of remission from seizures
- In a first epileptic seizure



Long-Term Mortality in Childhood-Onset Epilepsy

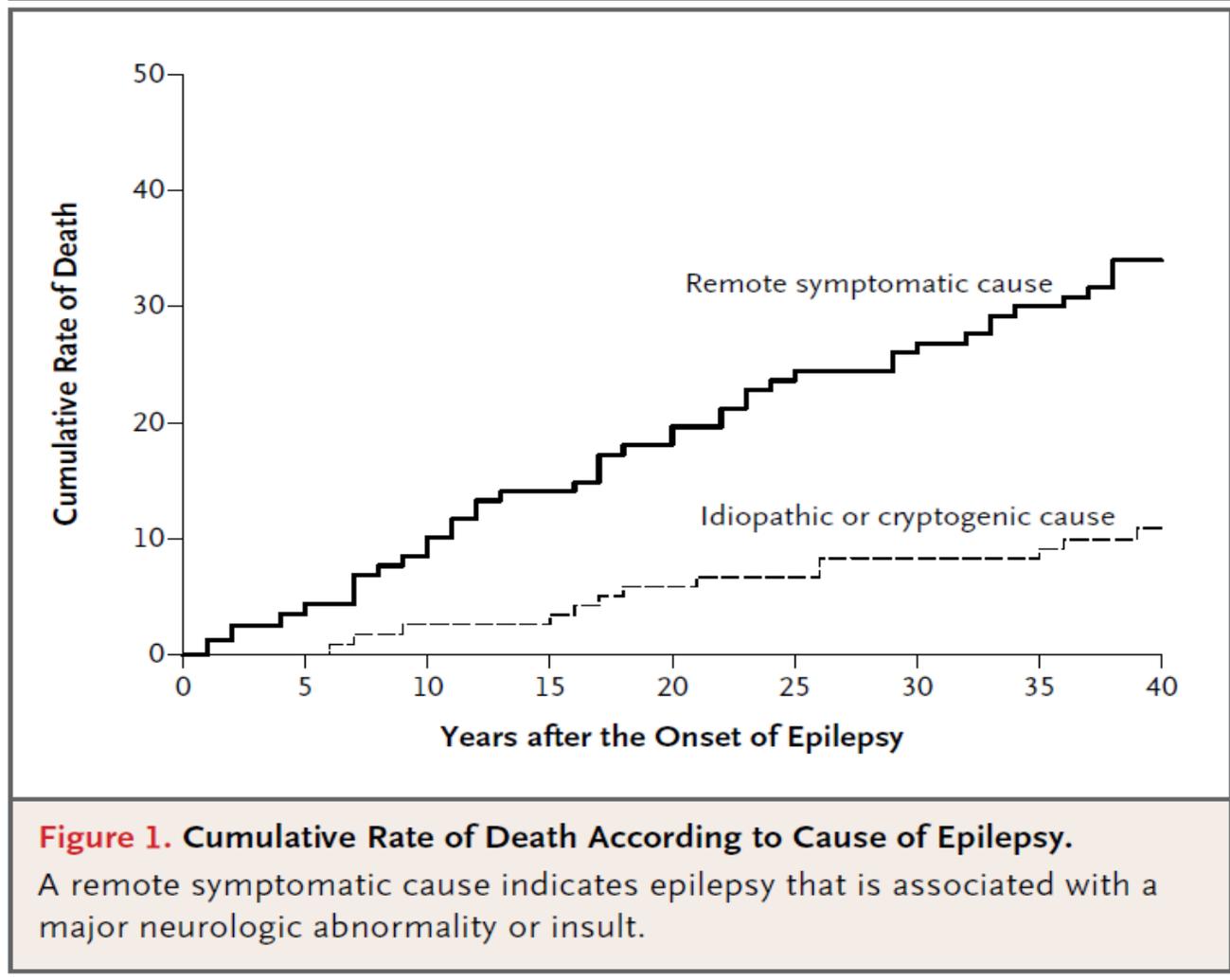
Matti Sillanpää, M.D., Ph.D., and Shlomo Shinnar, M.D., Ph.D.

- **245 patients with childhood epilepsy** identified from Finland's National Health Service registry (the entire population) and followed for 40 years. The majority (223 patients) were seen in Turku University Hospital.
- **24% of subjects died over the course of the study** (3X the expected mortality in the general population).
- 48% of those were < 5 years seizure-free at the time of death.
- **symptomatic epilepsy** (major neurologic impairment or insult) **increased the risk of death** vs idiopathic or cryptogenic cause (37% vs. 12%, $P < 0.001$).
- **55% of all deaths were related to epilepsy**
- Deaths not related to epilepsy occurred mainly in symptomatic epilepsy.

Long-Term Mortality in Childhood-Onset Epilepsy

Matti Sillanpää, M.D., Ph.D., and Shlomo Shinnar, M.D., Ph.D.

- **SUDEP 45% of all deaths** (with or without a definite or probable seizure; excludes drowning).
- Cumulative risk of SUDEP 7% at 40 years
- Cumulative risk of SUDEP 12% if **not in remission** > 5 years and **not taking medication**
- SUDEP was not observed in subjects with idiopathic or cryptogenic epilepsy, younger than 14 years of age.



The majority of deaths occur after adolescence.

This is consistent with reports that otherwise normal children with epilepsy do not have the same increased risk of death compared to the adult population (Nashef et al, Neurol Clin 2009)

SUPPLEMENT – 2007 ANNUAL COURSE

Should all patients be told about sudden unexpected death in epilepsy (SUDEP)? Pros and Cons

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PRO: Both the Scottish Intercollegiate Guidelines Network (SIGN) and the UK National Institute of Clinical Excellence (NICE) recommend universal discussion of SUDEP and support the view of one of the authors (MJB) and that of the Joint Epilepsy Council of UK charities that patients and their families have the right to know about the risks of epilepsy and the reasons for treatment.

CON: It is the contention of the other author (GLH) that it is not necessary or advisable, to discuss SUDEP with all patients.

- Risk of SUDEP is not uniform across all patient populations.
- Most people with newly diagnosed epilepsy will stop having seizures, and SUDEP is very rare among them.
- The mechanisms underlying SUDEP are unclear, and there are no effective preventative therapies. SUDEP should be discussed only with those patients who are at high risk. In particular, patients who have generalized tonic–clonic seizures and who are non-compliant with antiepileptic drugs should be counseled about their risk-taking behavior.

SUDEP: To discuss or not?

SUDEP: To discuss or not? Recommendations from bereaved relatives



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ABSTRACT

Purpose: The overarching purpose of this descriptive and exploratory qualitative study was to understand the experiences of relatives of individuals whose deaths were identified as SUDEP and to explore their preferences regarding SUDEP counseling.

Methods: The principles of fundamental qualitative description informed all design decisions. Stratified purposeful sampling included 27 bereaved relatives (parent, sibling, spouse or child), aged at least 18 years, of 21 persons who passed away because of SUDEP. In-depth one-to-one interviews were conducted. Directed content analysis was used to code, categorize, and synthesize the interview data.

Results: There was consensus among all participants that the risk of SUDEP should be discussed with patients by their healthcare providers. Relatives opted for information on SUDEP at the time of, or shortly following, the diagnosis of epilepsy. Neurologists were identified as the healthcare providers who should discuss SUDEP with patients during a face-to-face encounter, subsequently supplemented with written information. It was identified that, when discussing SUDEP, emphasis should be on the risk factors, possible preventive strategies, and the rarity of incidence.

Conclusion: The results of this study indicated that bereaved relatives wanted neurologists to inform patients about the risk of SUDEP, with optimal timing and setting of SUDEP counseling determined on a case-by-case basis.

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Measures for managing patients

Continually treat to an end point of no seizures. Especially keep tonic-clonic seizures to a minimum through optimal therapy and adherence.

Advise nocturnal supervision for high-risk patients - many deaths occur unwitnessed during sleep. Absence of supervision was identified as an important risk factor in one study of 154 cases of SUDEP with 616 controls.

The presence of supervision at night was found to be protective (OR: 0.4, 95% CI: 0.2 to 0.8) when a supervising individual shared the same bedroom or when special precautions such as a listening device were employed (OR: 0.1, 95% CI: 0.0 to 0.3). Langan et al., Neurology 2005; 64: 1131–33.

Advise patients to avoid the prone sleeping position. In an investigation from Norway 42 patients with definite SUDEP were reported, 25 died during sleep

17/24 were found dead in the prone position. There were positive signs of a seizure in 67% of the SUDEP cases.

Observe patients carefully after a tonic-clonic seizure until consciousness returns.

Counsel patients using a risk-benefit analysis as to lifestyle factors and treatment choices.

Measures for Managing Patients

Treatment changes:

1. Change in a gradual staged manner
2. Introduce the new drug before withdrawing the old drug
3. Ensure access to immediate advice in the event of worsening seizures during periods of change

Act on ictal warning signs:

1. Tonic-clonic seizures that are prolonged
2. Associated with marked cyanosis
3. Severe bradycardia or apnea
4. Post-ictal EEG suppression
5. Complex partial seizures with marked atonia (drop attacks)
6. Seizure in those with pre-existing cardiac or respiratory impairment

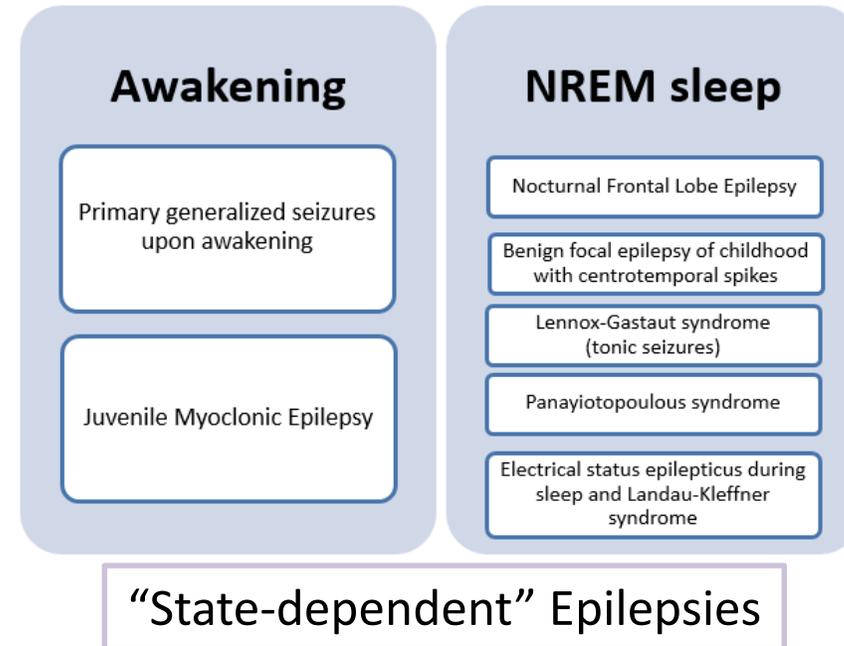
Unfortunately there is little medical evidence showing that SUDEP can be completely prevented by medical intervention.

SUDEP rates are reduced in patients who have undergone successful epilepsy surgery

What's New in Sleep and Epilepsy?

Some Epilepsy Syndromes Occur Primarily in Sleep or Upon Awakening

- A large prospective study found 7.5% of 1,200 patients had seizures restricted to sleep
- If a patient has SZs only during sleep > 2 years, unlikely to have a SZ awake (and could drive a motor vehicle even if not SZ-free)
- Only 11% of people with sleep-related SZs developed seizures when awake, typically within 2 years of the first nocturnal SZ
- Diurnal SZs in them were often triggered by sudden withdrawal of antiepileptic medication (AED)



Put 2/3 of Daily AED Dose at Night for Sleep-SZs Improved SZ Control

- Guilhou et al. (2011) treated 18 children with poorly controlled primarily nocturnal or early morning seizures by giving 2/3 of daily dose at night
- Of 18 patients treated this way, 11 were SZ-free at mean follow-up of 5 months, and 4 had 75-90% reduction in SZs

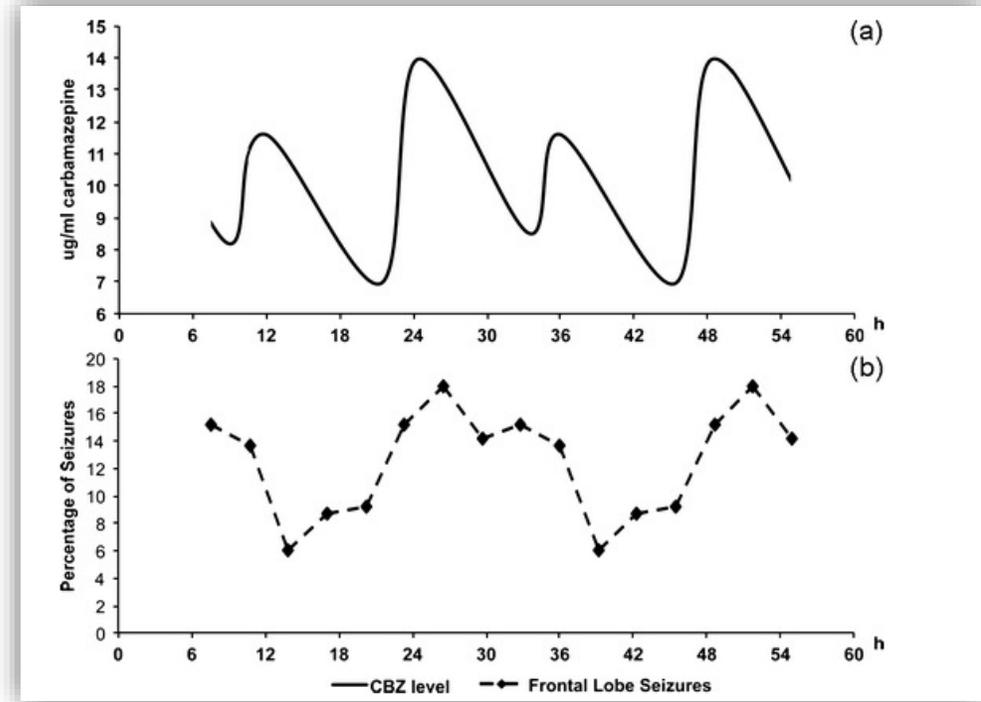


Figure a: Shows a solid line that depicts variations in plasma CBZ levels when patients received higher evening dose of CBZ. **Figure b:** Illustrates the percentage distribution of frontal lobe seizures over a 24-hour period, as demonstrated in a series of 41 consecutive pediatric patients.

Sleep Problems in Children with Epilepsy: 2-fold Higher than General Pediatric Population

Recent prospective case-control studies have shown:

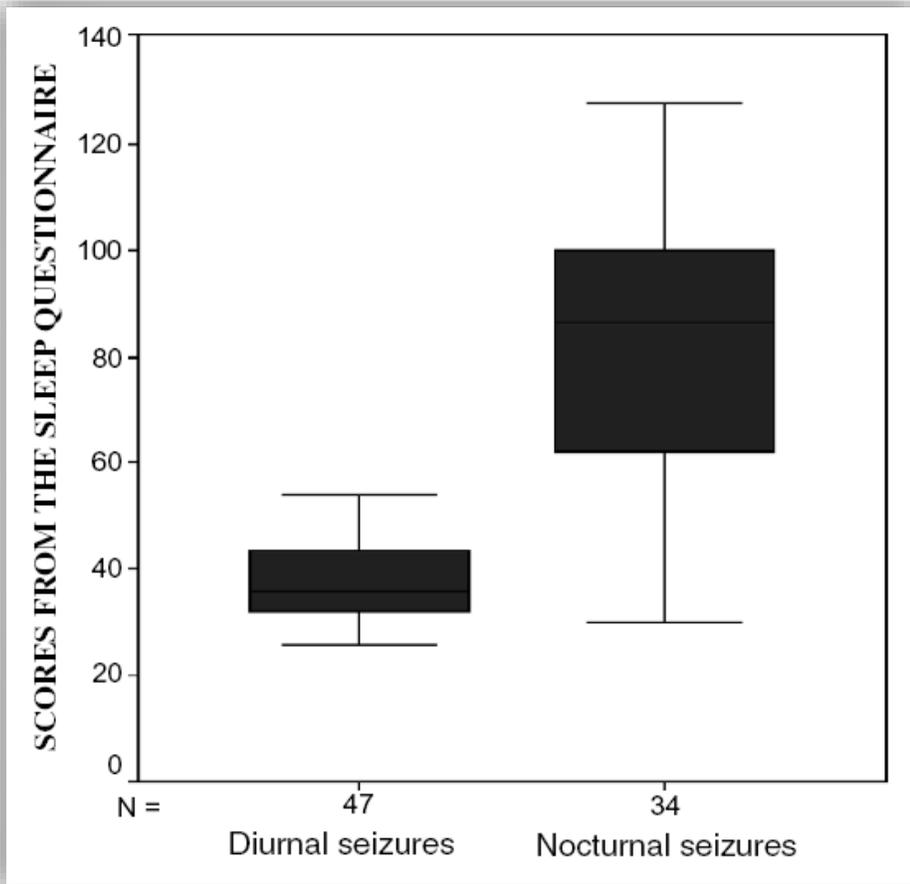
- 1) Severity of a child's epilepsy correlated with degree of child and parent sleep dysfunction and parental fatigue.^{1,2}
- 2) AED polytherapy predicted greater childhood sleep disturbances reported.^{1,2}
- 3) Nocturnal SZs, polytherapy, developmental delay, refractory epilepsy, generalized SZs, and epilepsy syndromes were unfavorable outcome associated with poor sleep habits.³
- 4) Children with epilepsy more likely to have poor sleep habits, especially if seizures primarily nocturnal, poorly controlled, and/or on AED polytherapy.³



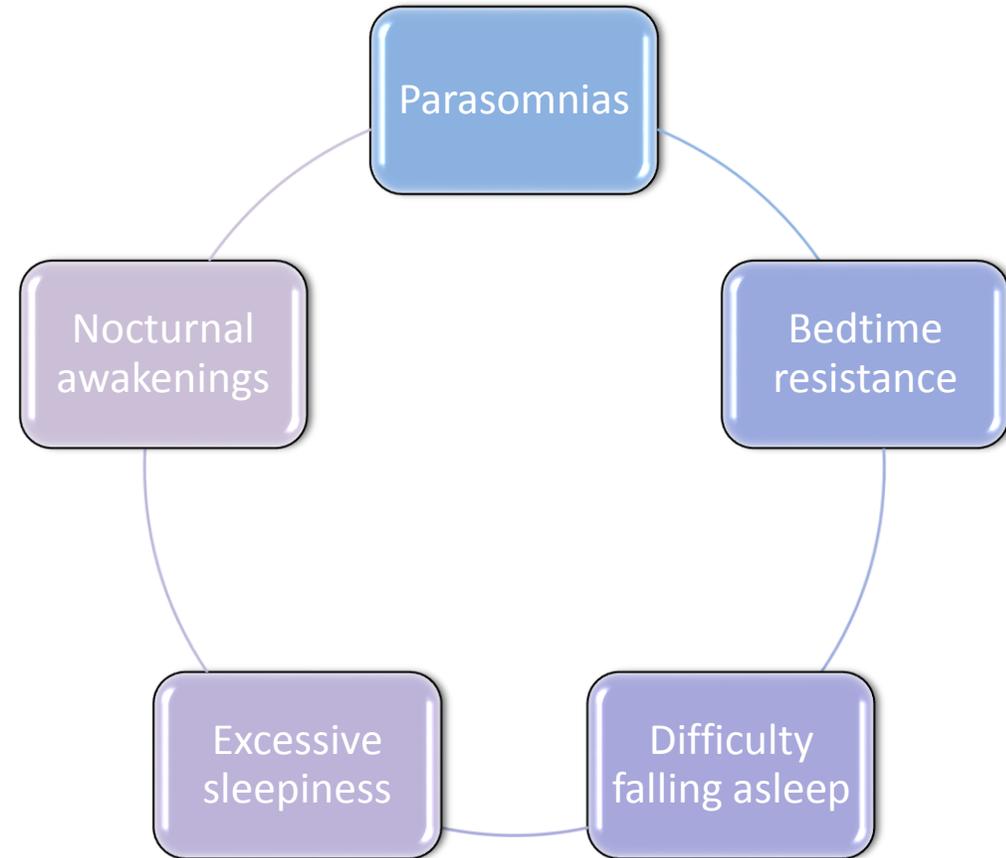
Sources:

1. Larson AM et al. *Epilepsia* 2012;53(7):1162-9
2. Williams J *Clin Pediatr (Phila)* 2000;39(11):635-42
3. Batista BH et al. *Epilepsy Beh* 2007;11:60-4

Sleep/Wake Complaints Much Greater in Children with Primarily Nocturnal SZs¹



Children with Epilepsy More Likely to Be Reported by Their Parents as Having²



Sources:

1. Batista BH et al. *Epilepsy Beh* 2007;11:60-4
2. Larson AM et al. *Epilepsia* 2012;53(7):1162-9

Parental Fear and Anxiety About SZ Recurrence Often Result in Return to Co-sleeping

- 22% of 179 children with epilepsy changed to less independent sleeping arrangements after epilepsy onset:
 - Compared to 8% of 155 children with juvenile diabetes.¹
- Co-sleeping does reduce risk for sudden unexpected death in epilepsy.



- However, another study found 62% of parents complained of decreased quantity and/or quality of sleep when co-sleeping and 44% reported rarely/never feeling rested because concerned about child having SZs during sleep.²

Sources:

1. Williams J Clin Pediatr (Phila) 2000;39(11):635-42
2. Larson AM et al. Impact of pediatric epilepsy on sleep patterns and behaviors in children and parents. Epilepsia 2012;53(7):1162-9

Sleep Problems in Children with Epilepsy Associated with ↓QOL and Behavior Problems

- 131 Dutch children (ages 4-10) with partial epilepsy and 161 age- and gender-matched controls:¹
 - Pathological scores on Sleep Disturbance Scale for Children 37% of CWE vs. 3% controls;
 - Significantly lower health QOL, lowest in children with epilepsy or controls who had sleep disturbances.
- Among 61 patients (ages 6-11) with benign childhood epilepsy with centrotemporal spikes:
 - Only patients who had SZs preceding 6 months were more likely to have sleep problems, longer sleep latency, and behavior problems.



Sources:

1. Gutter T et al. Subjective sleep disturbances in children with partial epilepsy and their effects on quality of life. *Epilepsy Behav* 2013;28(3):481-8
2. Samaitiene R et al. Sleep and behavior problems in children with rolandic epilepsy *Ped Neurol* 2013; 48(2):115-22

OSA More Common in Children with Epilepsy Whose SZs are Poorly Controlled, Treating Helps

- Prospective study 84 children with epilepsy (52 mild, 32 severe):¹
 - Uncontrolled epilepsy was risk factor for OSA (80%)
 - OAHl increased with increasing number of AEDs
- Retrospective study found treating OSA in 27 CWE (median age 5) often improved SZ control:²
 - Three months after adenotonsillectomy: 37% seizure-free, 11% >50% SZ-reduction.



Sleep Architecture More Disturbed in Medically Refractory on SZ-free Nights

- A prospective case-control study from India compared sleep architecture in 40 patients (median age 18) with epilepsy, 20 well-controlled; 20 medically refractory epilepsy
- Self-reported sleep parameters medically refractory vs. well-controlled characterized their sleep at home:
 - Longer sleep duration (9 h vs. 8 hours);
 - Daytime napping (2 h vs. 0 h);
 - Total 24-h sleep time (10.5 vs. 9 h);
 - EDS (45% vs. 10%);
 - Epworth scores did not identify (ESS > 10, 30% vs. 10%)

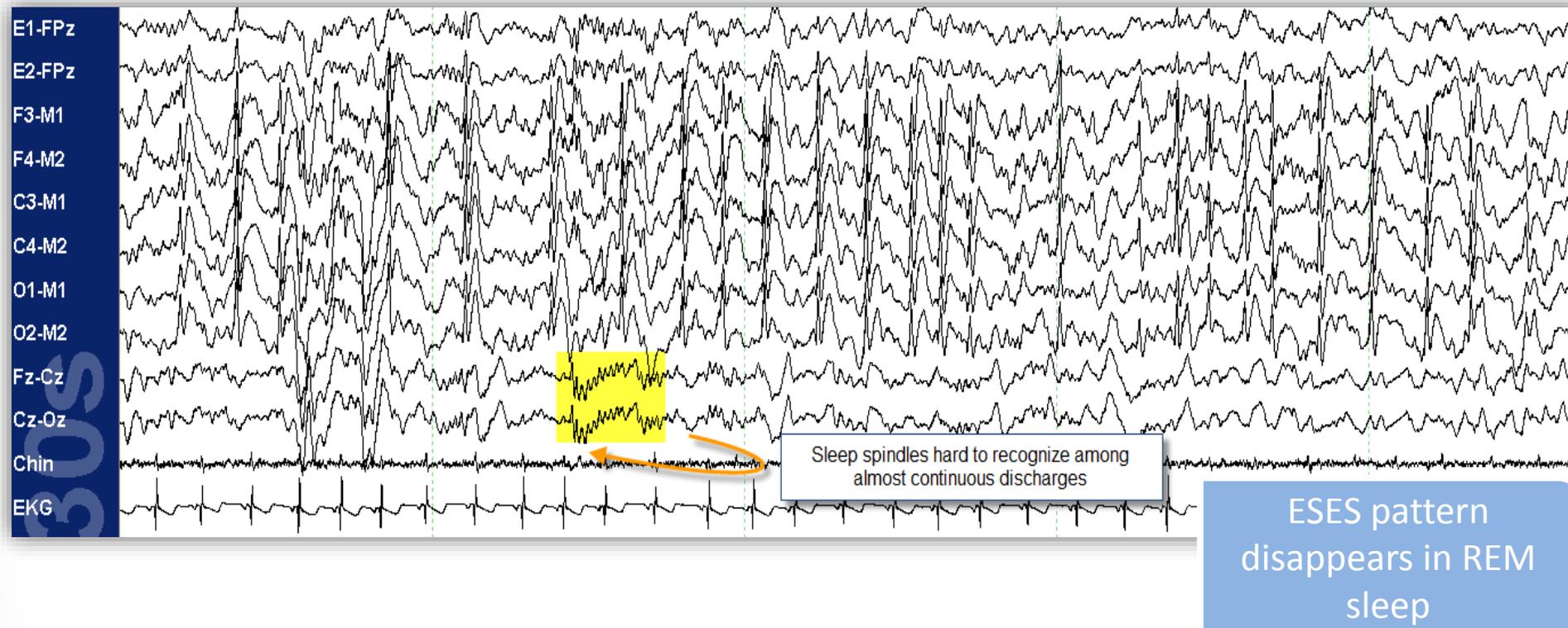


Does Sleep Architecture Improve if Seizures are Treated and Controlled?

- **Zanzmera (2013)** found improvements occurred in total sleep and REM sleep time 11 TLE patients SZ-free after epilepsy surgery¹
- **De Paolis (2013)** improved sleep architecture 12 NFLE patients after effective AED treatment (CBZ most, 2 TPM, 1 LEV)²
 - ↑ sleep efficiency (+10%), ↑ NREM 3 duration (+20 min)
 - ↓ REM sleep latency (-56 min); ↓ WASO (-35 min)
 - Still abnormalities in sleep architecture remained in those with NFLE Nevertheless, they still had longer REM sleep latencies, lower percentage of time spent in REM sleep, longer NREM 3 duration (+30 min) and percentage (+8%) than controls



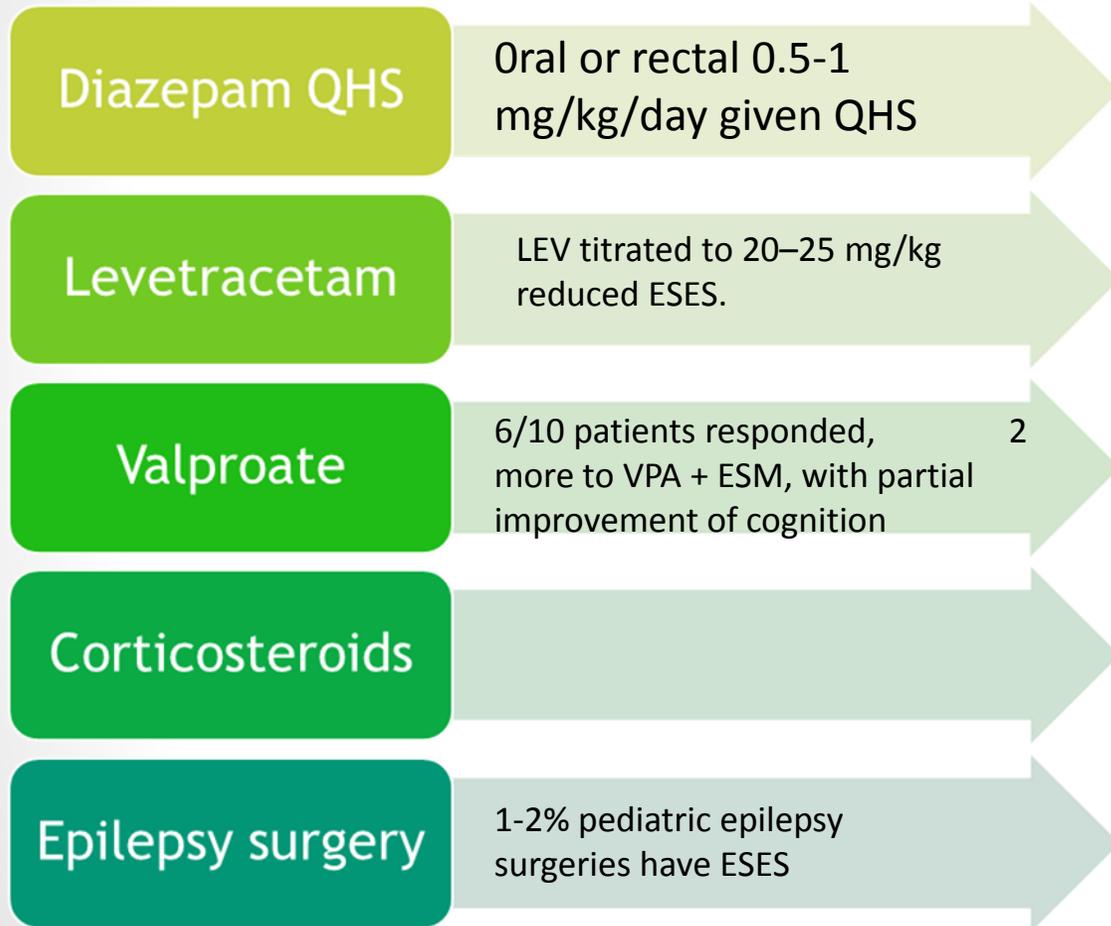
Encephalopathy with Electrical Status Epilepticus in NREM Sleep (ESES Syndrome)



A rare progressive epileptic encephalopathy of childhood characterized by:

- 1) Continuous spike-wave discharges in NREM sleep
- 2) Seizures
- 3) Global or selective regression of cognitive functions
- 4) Motor impairments (ataxia, dyspraxia and unilateral weakness)

Several AEDs Reduce ESES Spiking but Behavior and/or Cognition Does Not Improve in Most



• Corticosteroid regimen:

- Hydrocortisone: 5 mg/kg/day x month 1, 4 mg/kg/day month 2; he third month, and 2mg/kg/day during the next 9 months, followed by slow withdrawal for a total treatment duration of 21 months);
- ESES pattern often improves, but cognitive deficits may remain.
- **Lev** improves ESES pattern, but no significant improvement in cognition.

Avoid: CBZ or OXC (PHT and PB) can worsen SZs and cognition

High-dose Nocturnal DZP for Electrical Status During SWS

- 42 patients received high dose DZP (range 0.23 to 2.02 mg/kg/d);
- 69% had >50% reduction in spike index;
- Adverse effect were prevalent:
 - Some reports of problem-solving, and speech and writing development;
 - Sleep disturbances in 50%, irritability in 57%.
- Authors thought neurological and behavioral side effects in some individuals warrant further study.

Pediatric Neurology 50 (2014) 238–242

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Original Article

Medical Management With Diazepam for Electrical Status Epilepticus During Slow Wave Sleep in Children

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ABSTRACT

OBJECTIVE: Oral diazepam, administered in varying doses, is among the few proposed treatment options for electrical status epilepticus during slow wave sleep in children. We sought to retrospectively evaluate the long-term efficacy of high-dose oral diazepam in reducing electrographic and clinical evidence of electrical status epilepticus during slow wave sleep in children. Additionally, we surveyed caregivers to assess safety and behavioral outcomes related to ongoing therapy. **METHODS:** We collected demographic and clinical data on children treated for electrical status epilepticus during slow wave sleep between October 2010 and March 2013. We sought to identify the number of patients who achieved at least a 50% reduction in spike wave index on electroencephalograph after receiving high-dose oral diazepam. We also administered a questionnaire to caregivers to assess for behavioral problems and side effects. **RESULTS:** We identified 42 evaluable patients who received high-dose diazepam (range 0.23-2.02 mg/kg per day) to treat electrical status epilepticus during slow wave sleep. Twenty-six patients had spike reduction data and 18/26 (69.2%) children achieved a greater than 50% reduction in spike wave count from an average of 15.54 to 5.05 ($P = 0.001$). We received 28 responses to the questionnaire. Some patients experienced new onset of difficulties with problem-solving and speech and writing development. Sleep disturbances (50%) and irritability (57.1%) were the most frequent side effects reported. There did not appear to be a dose-related effect with electroencephalograph changes, behavioral effects, or side effects. **CONCLUSIONS:** High-dose oral diazepam significantly reduces the spike wave count on electroencephalograph in children with electrical status epilepticus during slow wave sleep. Although this therapy improves electroencephalograph-related findings, it can be associated with concerning neurological and behavioral side effects in some individuals, so further study is warranted.

Keywords: electrical status epilepticus during slow wave sleep, diazepam, children, seizure, status epilepticus

Pediatr Neurol 2014; 50: 238-242

Source

- Francois D et al. Ped Neurol 2014;50:238-42

Reproductive Health

- Teens with epilepsy are at high risk for unplanned pregnancy.¹
- AEDs can make hormonal contraceptives less effective.



Reproductive Health

Neural Tube Defects

- Valproic Acid

 1-2%

- Carbamazepine

 0.5%

Reproductive Health

- AEDs are teratogenic
 - Valproate = classic treatment for JME
 - Valproate = highest risk for teratogenicity
 - Consider levetiracetam or lamotrigine.
- Recommend folic acid daily
 - 5 mg per day



Bone Health



Bone Health

- Epilepsy = risk for poor bone mineralization
- Seizures = risk for falls & fractures

Risk Factors

- Deficient vitamin D intake
- Antiseizure medications
- Level of physical activity and ambulation
- Neuromotor dysfunction
- Overall nutrition



Vitamin D



- Vitamin D insufficiency is common.
 - 25-hydroxyvitamin D <32ng/mL
 - ~60% of all US children¹
 - ~75% of Michigan children with epilepsy²
- Risk factors: female sex, obesity
- All anticonvulsants implicated.
- All epilepsy syndromes implicated.



Sources:

- Kumar, et al. Pediatrics 2009;124:e362-70.
- Shellhaas & Joshi. Pediatr Neurol 2010; 42:422-426.
- Joshi, 2014

Suggested Vitamin D supplementation

25OHD level (ng/ml)	Vitamin D3 dose	Recheck labs	Additional labs
30+	400 IU per day*	Annually	
15-29	2000 IU per day in divided doses	Every 4 weeks until 25OHD >30**	Phosphorus, Magnesium, Calcium
<15	2000-4000 IU per day in divided doses, in consultation with dietician	Every 3-4 weeks until 25OHD >30**	PTH, Calcium, Magnesium, Phosphorus, Consider DEXA Scan

* In accordance with American Academy of Pediatrics recommendations, we suggest that all children treated for epilepsy be given a daily multivitamin with 400 international units of vitamin D3.

** Once 25OHD levels rise to the normal range, we halve the vitamin D supplement dose. If the level remains normal, recheck in 3-6 months.

