Epilepsy and Neurodevelopmental Disorders : Identifying and Managing comorbidities

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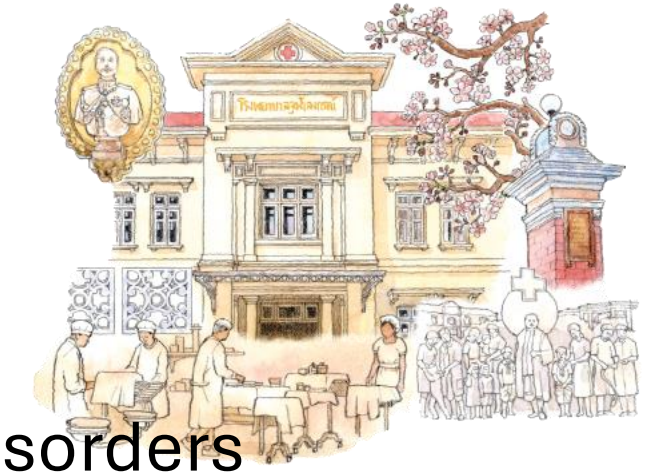
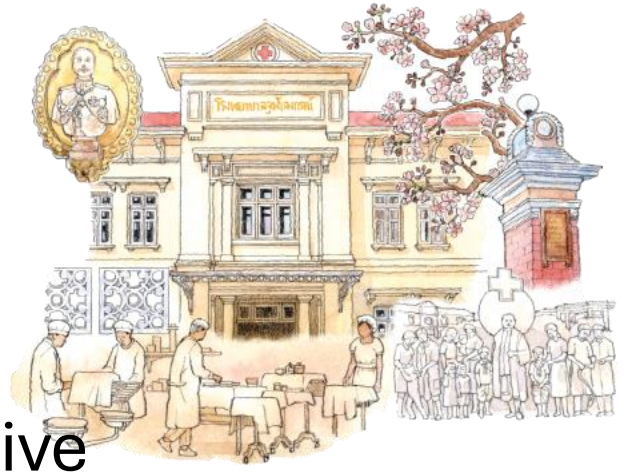
Introduction 1



- Epilepsy is one of the most common neurological disorders
- 20-30% of patients will continue to have ≥1sz per month
- They have negative effect on behavior and cognition

Introduction 2



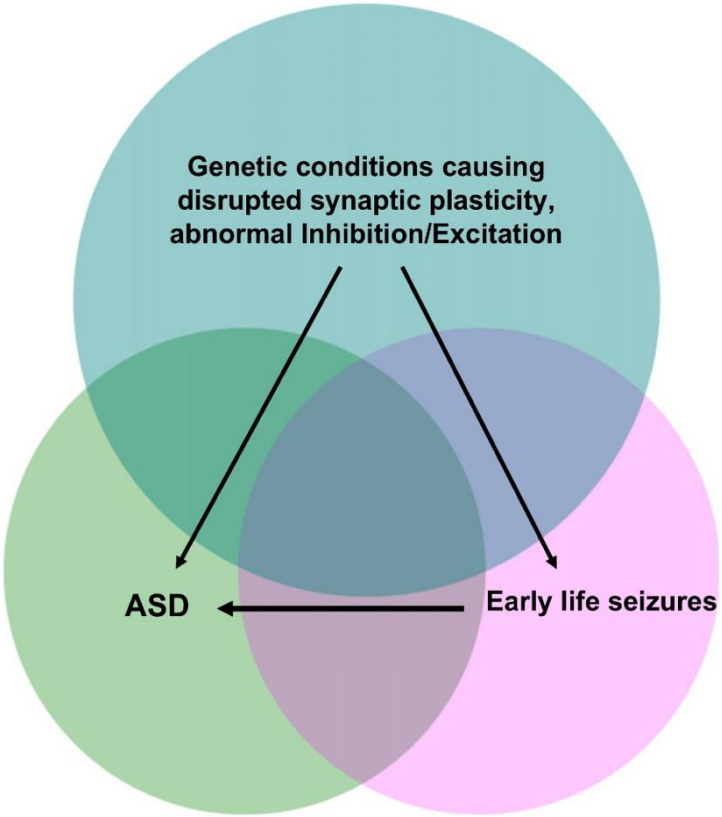
- ≥50% of children with epilepsy (CWE) have ≥1 cognitive /behavioral comorbidities
- ADHD more common in CWE (28-70%), inattentive type
- ASD in epilepsy 5-21%
- In turn, epilepsy in ASD range from 5-46% (in higher in severe ID)

Common comorbidities in children with epilepsy

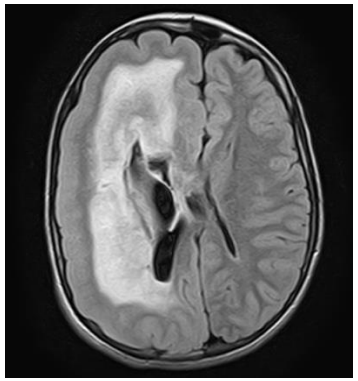
- Intellectual disabilities (ID)
- Autistic spectrum disorder (ASD)
- Attention deficit-hyperactivity disorder (ADHD)
- Specific learning disorders
- Anxiety
- Depression
- Sleep problem

Pathophysiological mechanism

- Disorder of synaptic plasticity
- Imbalance of excitation and inhibition in developing brain
- Genetic conditions associate with ASD and epilepsy: CDKL5 in West syndrome, MeCP2 in Rett syndrome, FMPR in fragile X syndrome, mTOR in TSC, and reelin in lissencephaly

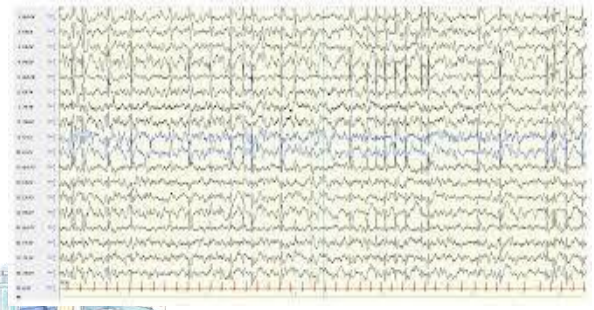


Factor associated with cognitive comorbidities



Underlying etiology

Epilepsy (age of onset) /epileptiform activity

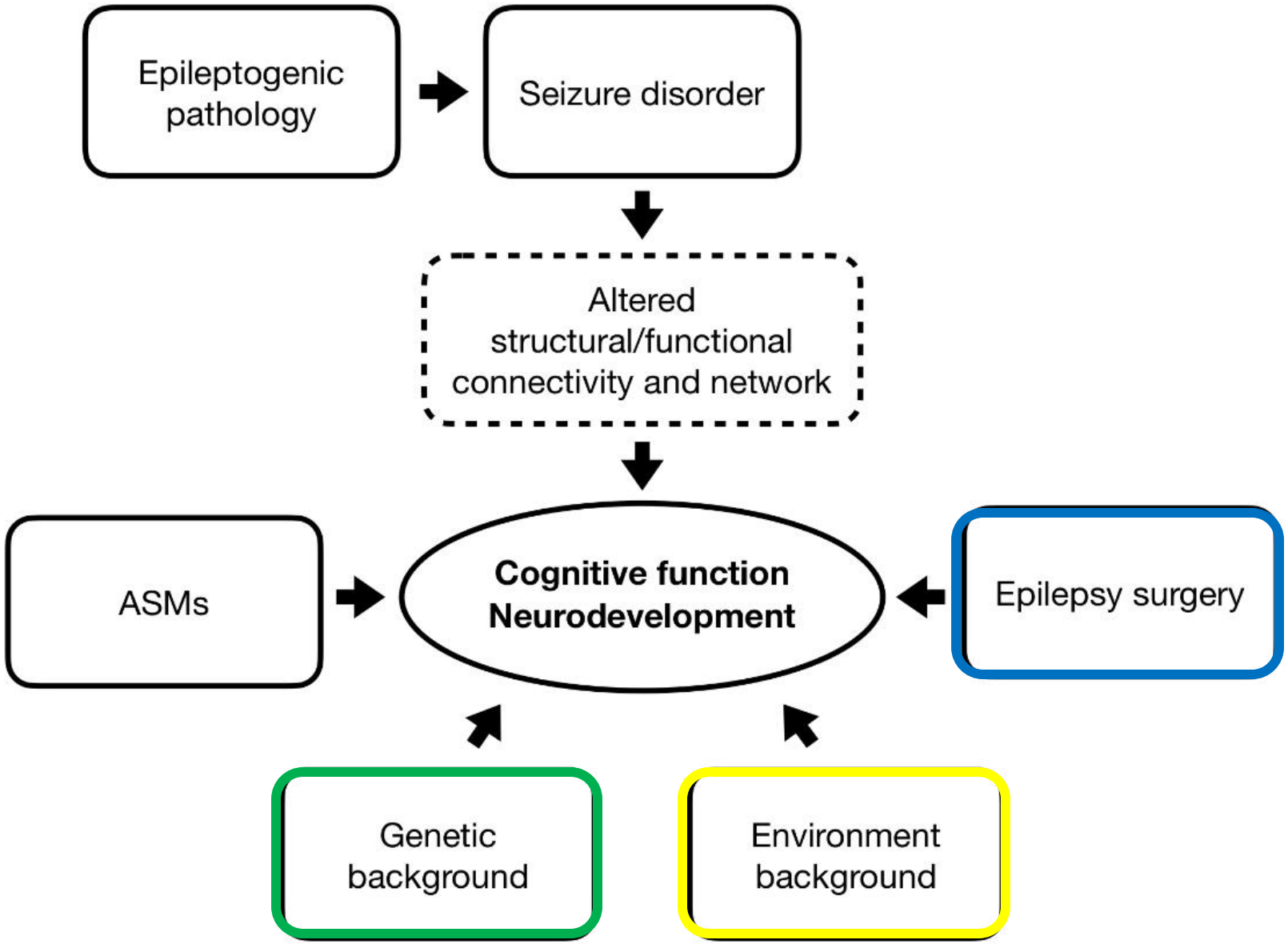


Antiseizuire medications

Cognitive/mental function

Other factors affecting cognition & behavior

- **Epilepsy etiology**
- **Age of onset** : early
- **Seizure type**: epileptic spasm, focal vs generalized
- **Frequency and duration**: frequent sz, high index of IEDs
- **EEG pattern**
- **Treatment response**


Epileptogenic pathology
Seizure disorder
Altered structural/functional connectivity and network
ASMs
Cognitive function
Neurodevelopment
Epilepsy surgery
Genetic background
Environment background

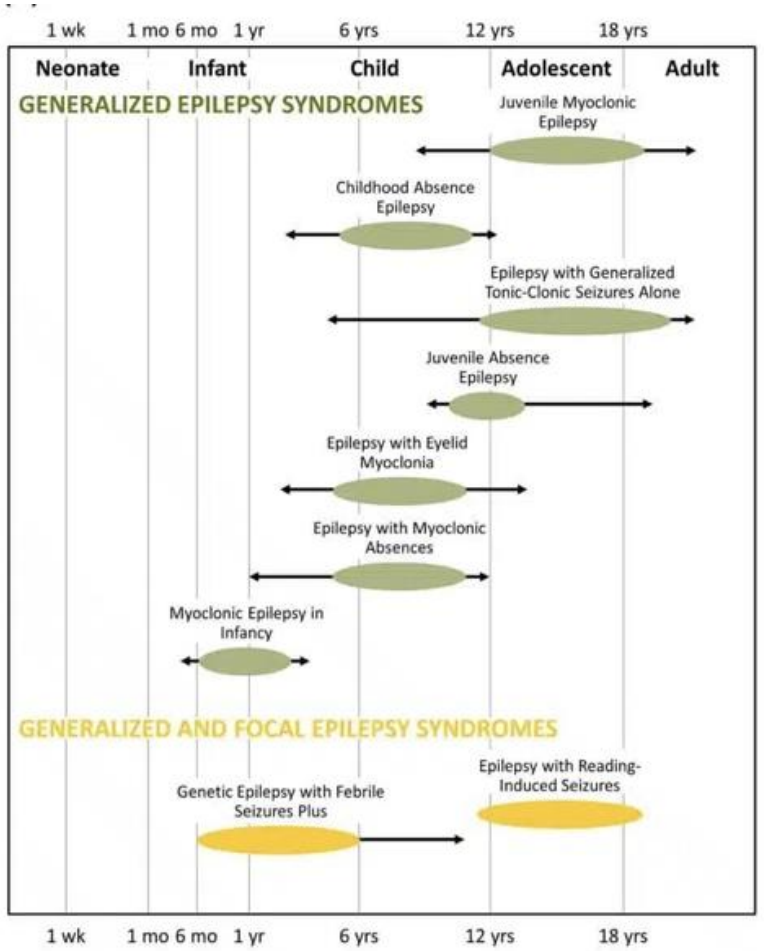
Epilepsy and cognition

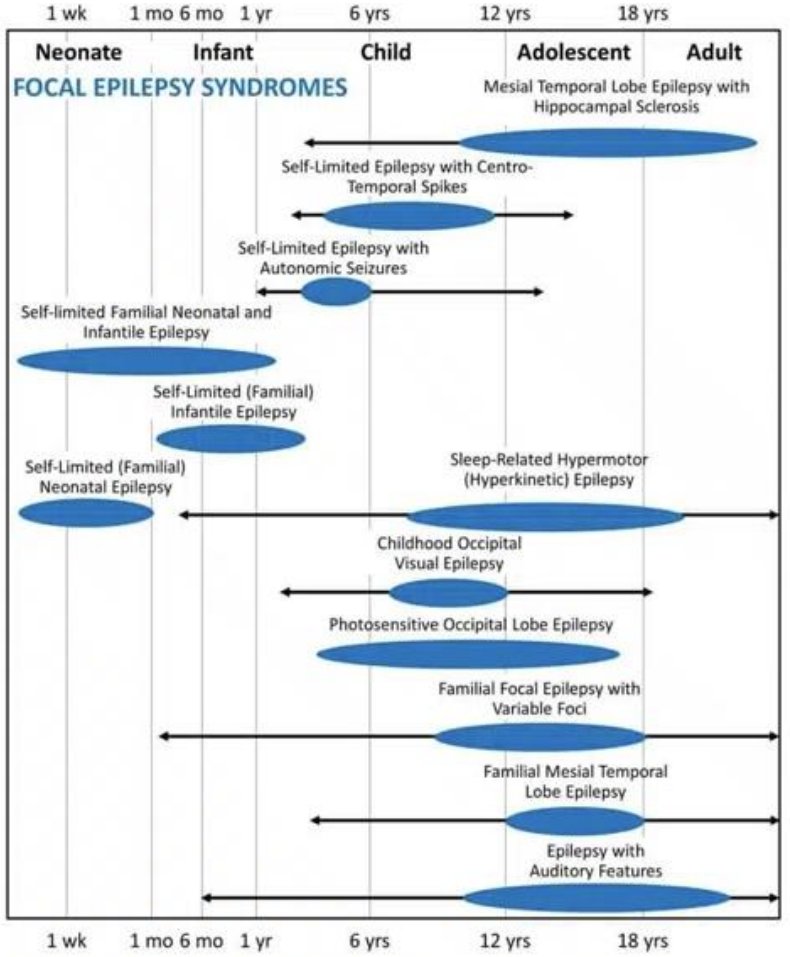
Etiology

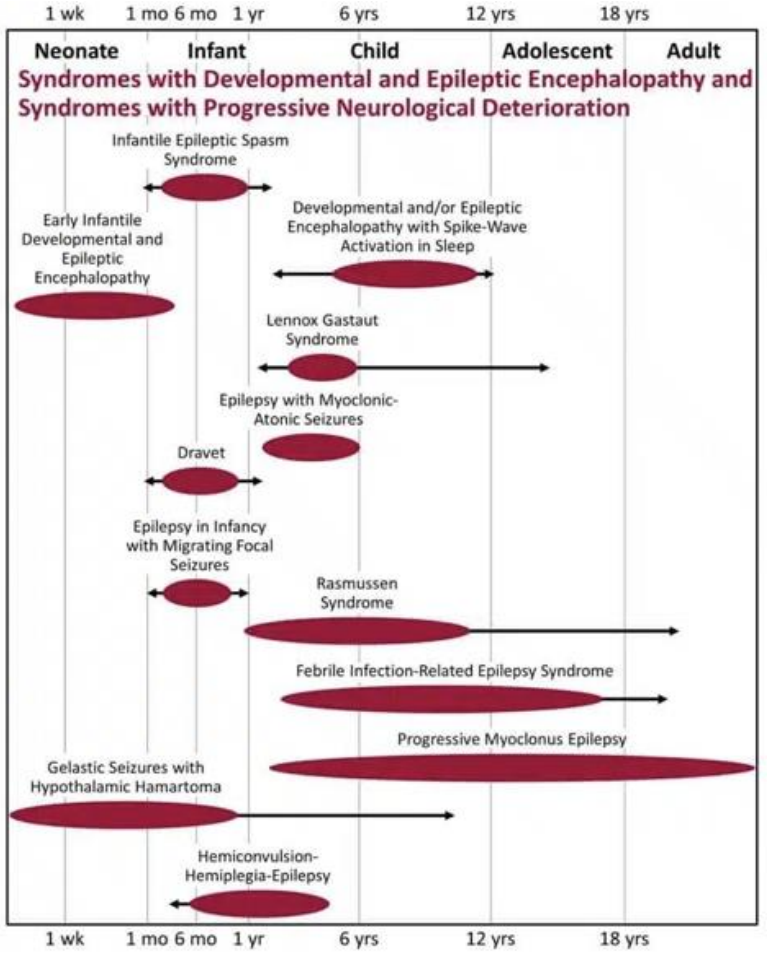
- Various genetic abnormalities (Rett syndrome, Angelman syndrome)
- Structural brain changes (MCD, HIE)
- Metabolic disorders (mitochondrial dysfunction, lysosomal storage diseases)

Effective Rx → Remarkable cognitive improvement

Epilepsy syndrome: Age of onset



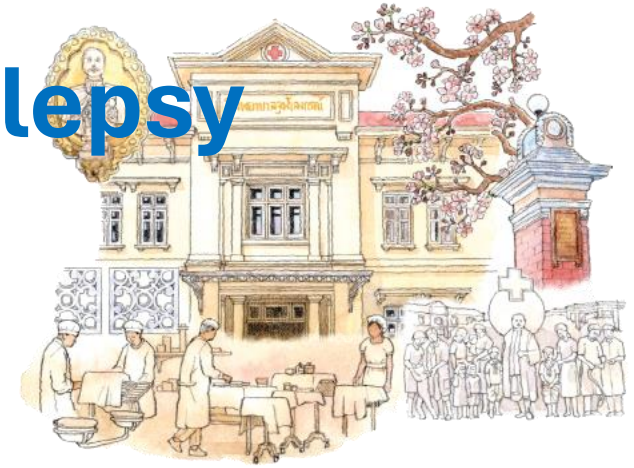




Epilepsia, 2022

Methodology for classification and definition of epilepsy syndromes with list of syndromes: Report of the ILAE Task Force on Nosology and Definitions

Psychiatric disorder in children with epilepsy



N=10438, age 5-15yo

British Child and Adolescent Mental Health Survey

Group (n)	*Percentage with psychiatric disorder (n)*				
	Any	*Emotional*	*Conduct*	*ADHD*	*PDD*
Complicated epilepsy (25)	56.0 (14)	16.0 (4)	24.0 (6)	12.0 (3)	16.0 (4)
Uncomplicated epilepsy (42)	26.2 (11)	16.7 (7)	16.7 (7)	0	0
Diabetes (47)	10.6 (5)	6.4 (3)	8.5 (4)	2.1 (1)	0
All other (10 202)	9.3 (946)	4.2 (427)	4.7 (483)	2.2 (228)	0.2 (25)

Any, any psychiatric disorder; Emotional, any emotional disorder; Conduct, any conduct disorder, including oppositional defiant disorder; ADHD, any attention-deficit–hyperactivity disorder; PDD, any pervasive developmental disorder (autistic disorder).

'Complicated epilepsy': with 1 or more of the following
Severe learning difficulties, cerebral palsy, any stiffness/deformities, any weakness, condition present since birth, any coordination difficulties, speech/language problem

Davies S, et al. Dev Med Child Neurol 2003

Pharmacoresistance and outcome

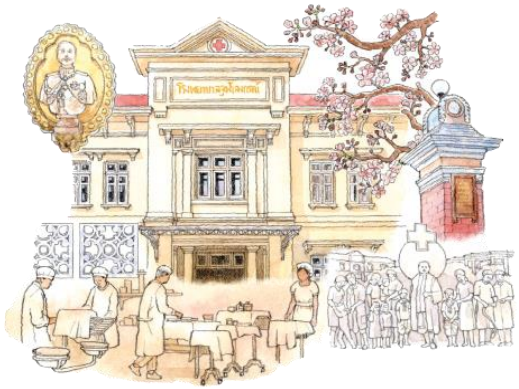
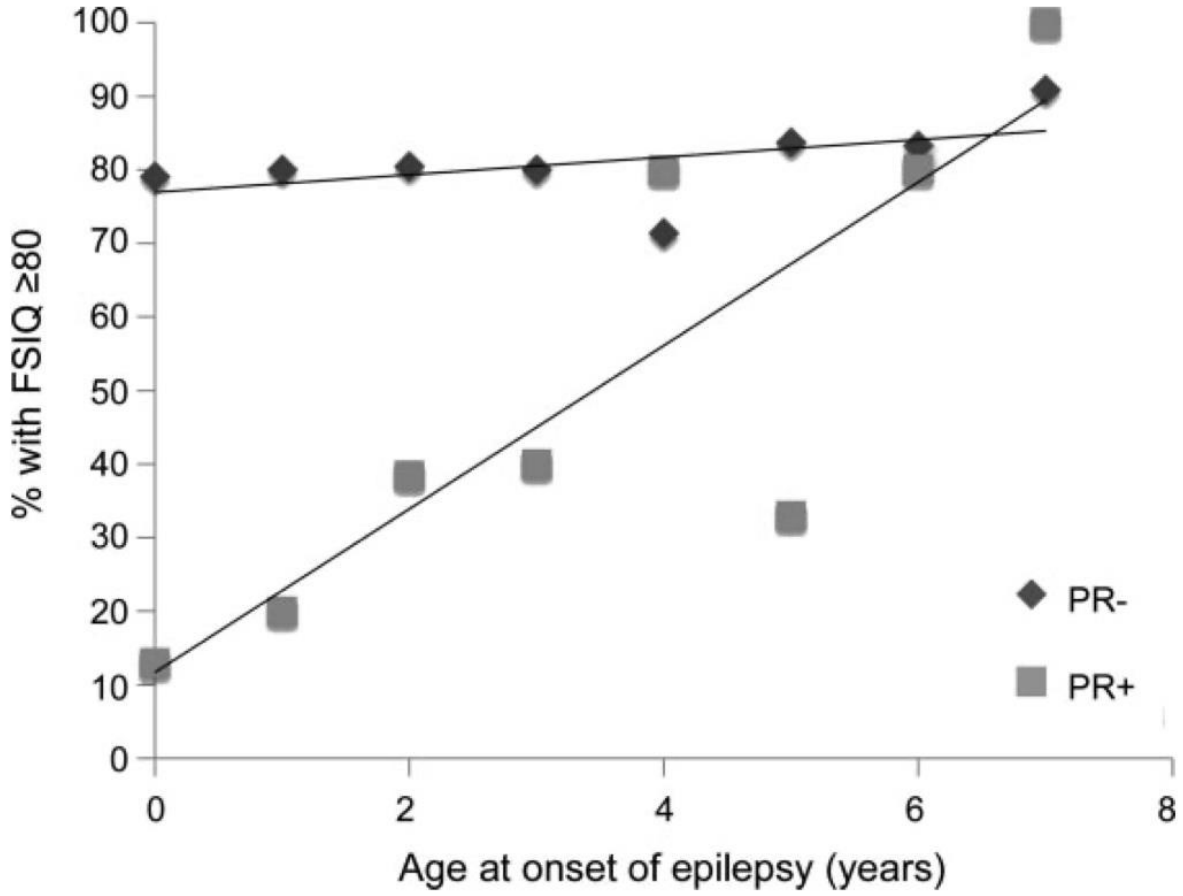


Figure 2 Full-scale IQ (FSIQ) ≥80 by age at onset and pharmacoresistance



- Longitudinal study (8-9 years follow up)
- New-onset epilepsy, age <8 y
- N=326

- No association between FSIQ and age at onset in PR- group
- PR+ group
  - 87% having FSIQ ≤80 for age <1y
  - 0% for age 7y

Original article

Cognitive effects of interictal epileptiform discharges in children

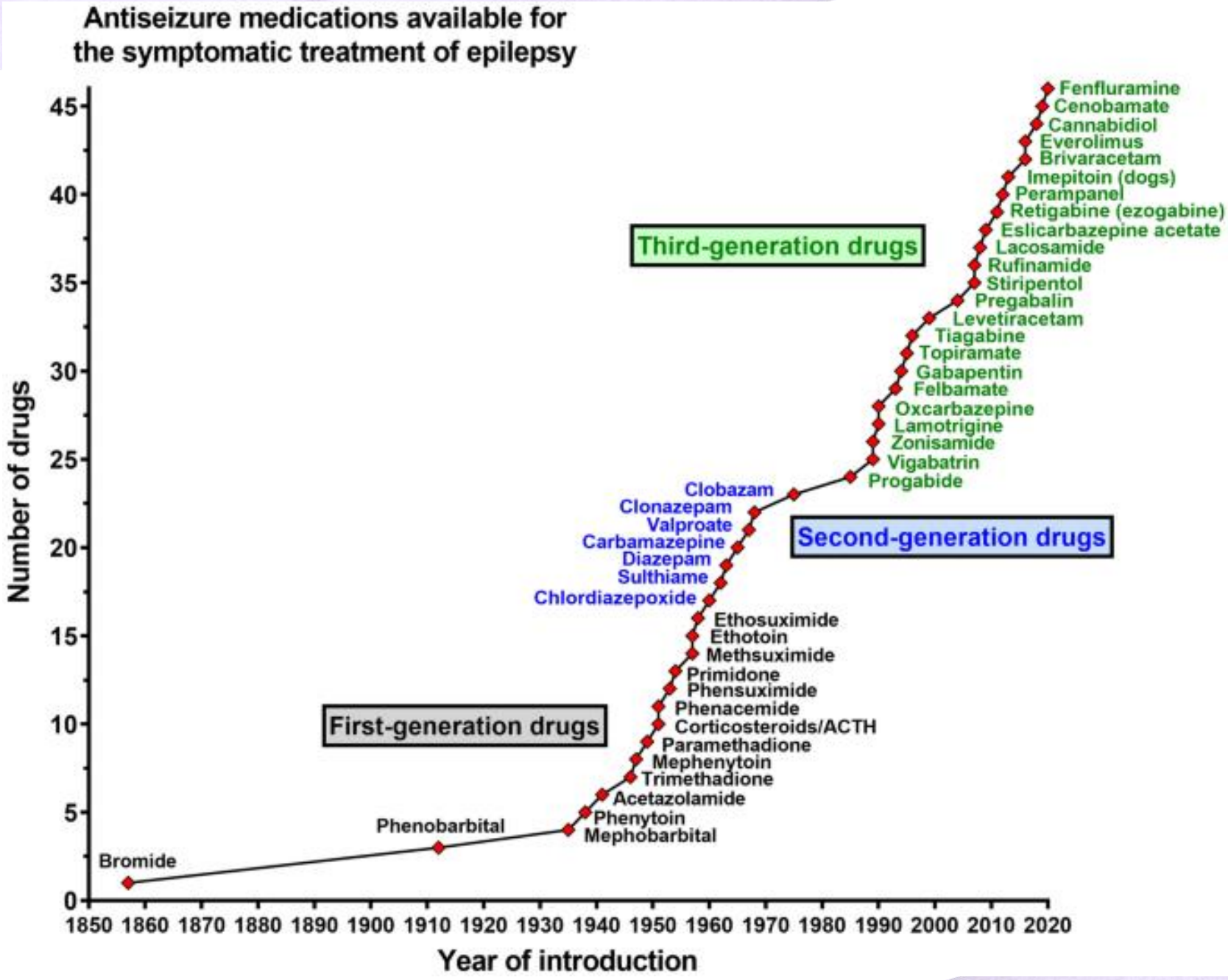
S. Ebus [a,*], J. Arends [a], J. Hendriksen [a], E. van der Horst [a], N. de la Parra [a], R. Hendriksen [a], E. Santegoeds [a], P. Boon [a,c], B. Aldenkamp [a,b]

European J Pediatric Neurology 2012

- Frequent IEDs may have effects on cognition
- Characteristics of IEDs
  - Frequency
  - Location: left-language, right-visuospatial
  - Occurrence: nocturnal-SeLECTs vs ESES
  - duration of runs
- Result: frequent IEDs >10% in awake EEG

  multifocal/generalized IEDs associate with impaired cognition

Antiseizure medications



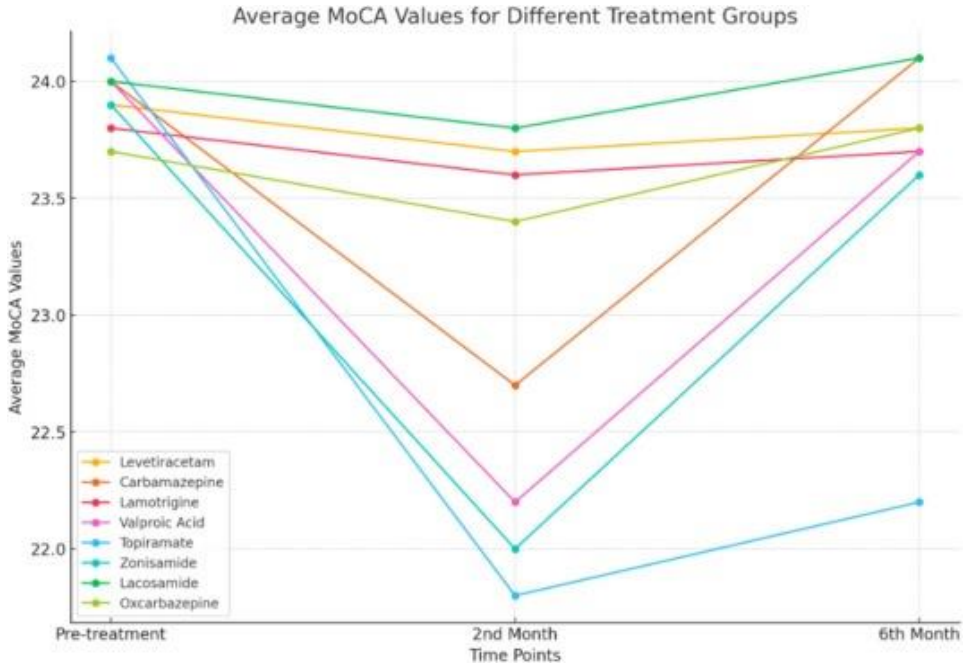
Antiseizure medications

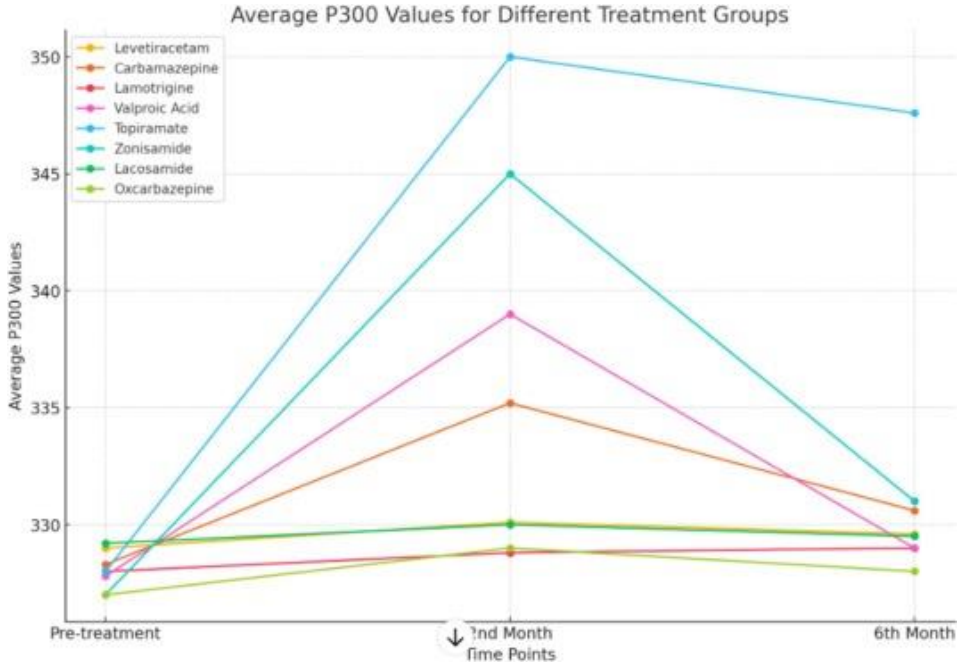
Research Paper

Assessment of temporal changes in cognitive effects induced by antiseizure medications in epilepsy patients

Ömer Karadaş [a,*], Javid Shafiyev [b], Akçay Övünç Karadaş [c], Uğur Burak Şimşek [b], Betül Özenç [d], Özlem Aksoy Özmenek [e]

Epilepsy&Behavior 2025





- N=254, age 18-50yo, initiating new ASM
- Using event-related potential, MoCA scores at 2, 6 mo
- At 2nd mo, CBZ, ZNS, VPA, and TPM showed significantly worse cognitive impairment compared to before
- LEV, LTG, LCM, and OXC showed no significant difference

Cognitive and Behavioral Comorbidities: An Unwanted Effect of Antiepileptic Drugs in Children

Semin Pediatr Neurol 2017

Adriana Ulate-Campos, MD,* and Ivan Sánchez Fernández, MD, MPH†,‡

Table Comparison of AEDs and Their Most Frequent Adverse Effects

AED	Aggression	Irritability	Somnolence	Deficits in Memory	Attentional Deficits	Suicidal Ideation
Carbamazepine	+	+	−	+	−	+
Clobazam	+	+	++	−	?	+
Ethosuximide	?	?	+	?	+	+
Gabapentin	++	++	+	?	+	?
Lacosamide	+	+	+	+	?	+
Lamotrigine	−	−	−	?	−	−
Levetiracetam	++	++	+	−	−	+
Oxcarbazepine	?	?	?	−	−	?
Perampanel	+	+	?	+	+	?
Phenobarbital	+	+	?	+	?	+
Phenytoin	?	?	?	+	?	?
Rufinamide	?	?	+	?	?	?
Sodium Valproate	+	+	+	?	+	?
Topiramate	+	+	?	++ Topiramate is associated with language deficits	?	?
Vigabatrin	+	+	?	?	?	?
Zonisamide	+	+	?	?	?	?

(+) means the mentioned adverse effect is present, (−) means it is not present, and (?) means it is not clear. This table is based on the revision of the currently available literature in children.

Teratogenic effect

Summary: ASM

- low cognitive risk: lamotrigine, levetiracetam
- higher cognitive risk: phenobarbital, topiramate, zonisamide
- Monotherapy and start low-go slow
- Consider: ketogenic diet, behavioral therapy, epilepsy surgery
- Investigational: gene therapy, ganaxolone, mTOR inhibitors

Approach to comorbidities detection

- Neuropsychological testing
- Screening questionnaires (parent/teacher reports)
- School performance
- MRI and EEG for specific syndromes or conditions

Neuropsychological testing

- Cognitive difficulties are often reported at diagnosis or before the first sz
- Problems can progress over time

Limitation

Type of epilepsy	Age to initiate screening	Recommended cognitive screening	Recommended frequency of repeat assessments
Early-onset epileptic encephalopathies • West syndrome • Dravet syndrome • Myoclonic atonic epilepsy • Lennox–Gastaut syndrome	Preschool	Comprehensive neuropsychological evaluation	• Detailed history of development every 6–12 months • Follow-up comprehensive neuropsychological evaluations every 2–3 years*
Other epilepsies with infantile/preschool onset and developmental delay	Preschool	Comprehensive neuropsychological evaluation	• Detailed history of development every 6–12 months • Follow-up comprehensive neuropsychological evaluations every 2–3 years*
Other epilepsies with infantile/preschool onset without obvious developmental delay	Preschool	History of developmental milestones, +/- parent-completed scales (Vineland; BRIEF, Achenbach); if either indicates delayed development, proceed to comprehensive neuropsychological evaluation	• Every 6–12 months
Genetic generalized epilepsies • Childhood absence epilepsy • Juvenile absence epilepsy • Juvenile myoclonic epilepsy	At diagnosis	History of developmental milestones, +/- parent-completed scales (Vineland; BRIEF, Achenbach); if either indicates delayed development, proceed to comprehensive neuropsychological evaluation	• Every 12 months
Benign focal epilepsies of childhood (benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome)	At diagnosis	History of developmental milestones, +/- parent-completed scales (Vineland; BRIEF, Achenbach); if either indicates delayed development, proceed to comprehensive neuropsychological evaluation	• Every 12 months
Focal epilepsies of known cause	Preschool, (or if onset at later age, at diagnosis)	History of developmental milestones, +/- parent-completed scales (Vineland; BRIEF, Achenbach); if either indicates delayed development, proceed to comprehensive neuropsychological evaluation	• Every 6–12 months • Children with medically intractable focal epilepsy should undergo comprehensive neuropsychological evaluation with follow-up every 2–3 years • Comprehensive neuropsychological testing should also be performed prior to resective epilepsy surgery
Other focal epilepsies of unknown cause	Preschool, (or if onset at later age, at diagnosis)	History of developmental milestones, +/- parent-completed scales (Vineland; BRIEF, Achenbach); if either indicates delayed development, proceed to comprehensive neuropsychological evaluation	• Every 6–12 months • Comprehensive neuropsychological testing should also be performed prior to resective epilepsy surgery
Epileptic encephalopathy with CSWS or Landau–Kleffner syndrome	At diagnosis	Comprehensive neuropsychological evaluation with formal speech and language evaluation	• Detailed history of development every 6–12 months • Follow-up with comprehensive neuropsychological evaluations every 2–3 years*
Other epilepsies with a significant risk of neurocognitive problems • Rasmussen encephalitis • Other immune-mediated epilepsies • Epilepsies caused by inborn errors of metabolism or specific genetic abnormalities	At diagnosis	Comprehensive neuropsychological evaluation	• Detailed history of development every 6–12 months • Follow-up with comprehensive neuropsychological evaluations every 2–3 years*

*Ideally, neuropsychological testing should be repeated after 2 years initially, and then every 3 years until the child has completed school. Neuropsychological evaluation may be deferred if the child has profound developmental delay. In syndromes in which remission may occur (myoclonic atonic epilepsy, Landau–Kleffner syndrome, epileptic encephalopathy with continuous spike-and-wave discharges during slow-wave sleep (CSWS), further evaluations are not required if the child has normal development at the time of remission. BRIEF, Behavior Rating Inventory of Executive Function.

Katherine C. Nickels et al, Nat Review Neurol 2016

Options for screening: questions at visit

- Decline in academic performance
- Attention and concentration problems
- Difficulties completing schoolwork at home
- Behavioral and emotional problems
- Refusal to attend school

Referral for formal neuropsychological testing, if concerns are raised

Management

- Screen early and regularly
- Tailor ASM to minimize cognitive impact
- Collaborate with school and therapy services
- Treat ADHD, mood, and behavior if present

Sleep

Sleep & epilepsy

- Sleep deprivation lowers sz threshold
- Cause a rebound increase in N3 stage -> slow thalamocortical oscillation -> may associated with epileptogenesis
- Risk of OSA is higher in patient on >1 ASM
- Epilepsy also affects sleep: more arousal, more REM

Sleep & epilepsy in autism

- Sleep disturbance in ASD estimates ranging from 40-80%
- OSA may not affect children with ASD more than ped population
- As many as 30% of ASD have EEG abnormalities or clinical sz
- Child with ASD and disrupted nighttime sleep and EEG abnormalities – challenging
- Interictal spk during REM and slow-wave sleep interfere with consolidation of memories

Sleep and risk of SUDEP

- 'Non-traumatic, non-drowning, unexpected death in healthy person with epilepsy'
- Incidence 1 per 1000 person year (1% per year in refractory epilepsy)
- Most frequent in ages of 15-40 y
- 40-60% are sleep-related
- Mechanisms: unknown
- Possicle factors: prone position, OSA

Assessment of sleep

Collect history

- The past medical history, birth and developmental information, psychosocial background and family history of a child
- Comorbid conditions associated with sleep-related symptoms
- A thorough sleep history with a complete characterization of the presenting complaint, bedtime routines, details about the sleep environment and nocturnal and daytime behaviours
- Past medication prescribed for or that impacted sleep, current medications and any allergies

Physical examination

Mainly for suspicion of obstructive sleep apnoea syndrome (OSA): obesity assessment; facial dysmorphism as in Down Syndrome

Blood work investigations

Needed for ruling out inflammation and biochemical imbalances, such as iron or vitamin D3 deficiencies

Validated questionnaires and structured interviews (Table 1)

Helpful in the structured assessment of sleep problems and useful in evaluating treatment response

Sleep logs

- The complete sleep–wake schedule, noting bedtime, sleep time, awakenings during the primary sleep bout, wake time, and timing of additional sleep bouts for the patient
- Sleep logs should be collected for at least 7 days but preferably ≥14 days

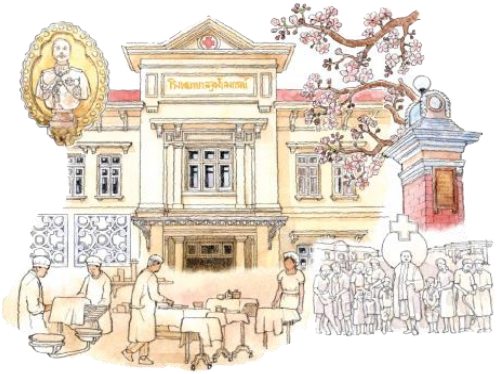
Actigraphy

- Unobtrusive, relatively inexpensive, prolonged monitoring for approximating sleep–wake cycles
- A small, lightweight accelerometer within a wristwatch-like compartment to record and integrate limb movement activity over time and often collect additional data such as light levels and skin temperature
- Recommended by the American Academy of Sleep Medicine (AASM) for the evaluation of paediatric patients with insomnia, circadian rhythm sleep–wake disorder or suspected central disorders of hypersomnolence

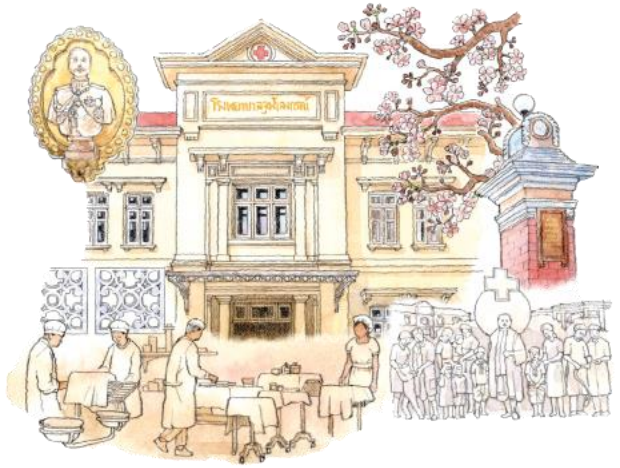
Polysomnography

- To provide detailed information regarding sleep architecture, cardiorespiratory parameters, isolated or whole-body movements, and arousals during sleep
- A standard recommendation by AASM for polysomnography following adenotonsillectomy to assess for residual OSA in children with neurodevelopmental disorders among other criteria
- To evaluate suspected periodic limb movement disorder or other causes of hypersomnia; to confirm a diagnosis of an atypical or potentially injurious parasomnia; to differentiate a parasomnia from sleep-related epilepsy

Key Takeaways



- Neurodevelopmental comorbidities: common and impactful
- Seizure control ≠ cognitive recovery
- Early screening, syndrome recognition, and tailored therapy are essential



Thank you