# EPILEPTIC ENCEPHALOPATHIES OF CHILDHOOD

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I receive honoraria from Lundbeck ( Sabril and Onfi) and from Eisai (Banzel)

# EPILEPTIC ENCEPHALOPATHY

- "embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone"
- …"and these can worsen with time"

Report of the ILAE commission on classification and terminology, 2005-2009, Epilepsia: 2010

## EPILEPTIC ENCEPHALOPATHY

- Interplay between underlying pathophysiologic substrate
- Acquired consequences of frequent and repetitive seizures and interictal discharges that straddle the borderland between interictal and ictal activity.
- Disruption of distributed neural networks that underpin cognitive functions, both temporarily and permanently

## EPILEPTIC ENCEPHALOPATHIES

- Heterogeneous group of disorders
- Occur at a critical period of brain development
- EEG discharges may occur only during sleep (sleep activation) or potentiate in sleep (sleep potentiation)
- Epileptic activity interferes with the development and organization at the immature brain and with cognition
- Epileptiform activity may become persistent, perpetuating hyper-excitability, altering networks, seizure semiology (focal or generalized) and response to treatment
- E.g. West Syndrome evolving to Lennox Gastaut Syndrome (LGS)

## EPILEPTIC ENCEPHALOPATHIES

- **Neonatal:**
  - Early myoclonic encephalopathy (EME)
  - Ohtahara syndrome
- **Infancy:**
  - Epilepsy of infancy with migrating focal seizures
  - West syndrome
  - Dravet syndrome
  - Myoclonic epilepsy in non-progressive disorders
- **Childhood:**
  - Epileptic encephalopathy with continuous spike-and-wave during sleep (csws, including Landau-Kleffner syndrome) and Lennox-Gastaut syndrome
- **Other severe epileptic encephalopathies:**
  - Kozhevnikov-Rasmussen syndrome, fever induced refractory epileptic encephalopathy (FIRES)
  - Hemiconvulsion- hemiplegia-epilepsy syndrome (HHE)

## WEST SYNDROME

- Slight bobbing's of the head forward
- Increased in frequency and at length became so frequent and powerful as to cause a complete heaving of the head forward to the knees (emprosthotonus)
- 10 to 20 or more times at each attack, which attack would not continue more than 2 to 3 minutes
- Two, three or more attacks in a day.

On a peculiar form of infantile convulsion

William West, 1841

## WEST SYNDROME

- ".....lack of language and meaningless laughter….and rolling of the head"
- "…..delighted by music and gay colors"
- "……a great tendency to automatism and rhythmical actions"

-Langdon-Down

## WEST SYNDROME

- Triad of clustered spasms, hypsarrhythmia on EEG, delayed development or regression
- 2-5 per 10,000 newborns
- Peak between 4 -7 months
- Duration 25-32 months, 50% cease by 2 years of age, 75% by 6 years of age

## WEST SYNDROME

- Structural-metabolic (symptomatic) or cause unknown (cryptogenic)
- UKISS
  - Hypoxic ischemic encephalopathy (10%)
  - Chromosomal anomalies (8%)
  - Perinatal stroke (8%)
  - Tuberous sclerosis complex (7%)
  - Periventricular leukomalacia or hemorrhage (5%)

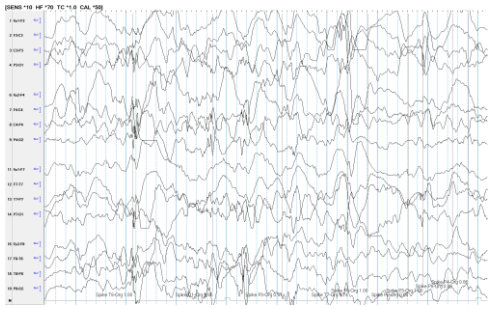
## INFANTILE SPASMS

- Initial phasic component (< 2 seconds), more sustained but less intense tonic component (up to 10 seconds)
- Flexor, extensor, mixed extensor-flexor
- Subtle spasms: yawning, grasping, facial grimacing, isolated eye movements, blinking
- Asymmetric spasms
- 80% occur in clusters
- Focal versus generalized

## HYPSARRHYTHMIA

- "… Random high voltage slow waves and spikes. These spikes vary from moment to moment."
- "At times they appear focal, and a few seconds later they seem to originate from multiple foci"
- "Never appears as a rhythmically repetitive and highly organized pattern that could be confused variant, with a discharge of the petit-mal type
- Abnormality is almost continuous and in most cases it shows as clearly in the waking as in the sleeping record

## HYPSARRHYTHMIA



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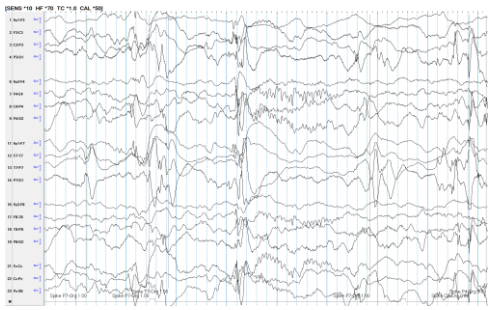


## UNITED KINGDOM INFANTILE SPASMS STUDY

- Multicenter, randomized controlled trial, 150 UK hospital
- Vigabatrin (100mg/kg/day) versus oral prednisolone (40mg/day) or intramuscular tetracosactide depot (40 I.U.)
- Primary outcome- cessation of spasms on day13/ day14
- 40/55 (73%) spasm free: steroid group
- 28/52 (54%) spasm free: vigabatrin group

Lancet, 2004

## INFANTILE SPASMS: EVIDENCE FOR EPILEPTIC ENCEPHALOPATHY

- Children whose treatment is delayed by 2 months have a developmental quotient 16 points lower than those treated promptly
- Down syndrome: median 1Q of 37 in those treated within 2 months of onset, median 1Q of 14 with delayed treatment
- Pre-treatment with vigabatrin in infants with TS at earliest detection of IED's, prior to onset of spasms or focal seizures, associated with significantly improved developmental outcomes

## LENNOX GASTAUT SYNDROME (LGS)

- 'Petit mal variant''; Gibbs et al 1939
- Triad of symptoms including generalized SSW, mental deficiency and multiple seizure types; Lennox and Davis, 1950
- Childhood epileptic encephalopathy with diffuse slow spike waves (otherwise known as petit mal variant) or Lennox syndrome; Gastaut et al., 1966

## LENNOX GASTAUT SYNDROME (LGS)

- Triad of multiple seizure types, slow spike wave (paroxysmal fast activity) and slow mental development
- Age dependent: 1 to 8 years (3 to 5 years)
- Structural-metabolic, cause- unknown
- 10% to 25%, preceding infantile spasms
- Overlap between the EEG patterns of hypsarrhythmia, slow spike wave activity, and independent multifocal slow spike wave discharges

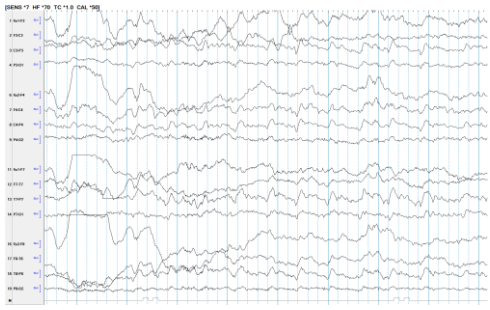
## LGS – THE SEIZURE TYPES

- Drops, nod, blinks, jerks
- Drop attacks; (33%-66%)
- Tonic seizures (75%): neck and trunk flex, arms raise, facial and masticatory muscles contract, sursum deviation of eyes
- Atypical absences (75%): onset and offset not as clear; drooling, changes in postural tone, eyelid-peri-oral myoclonia
- Status epilepticus; (3/4)

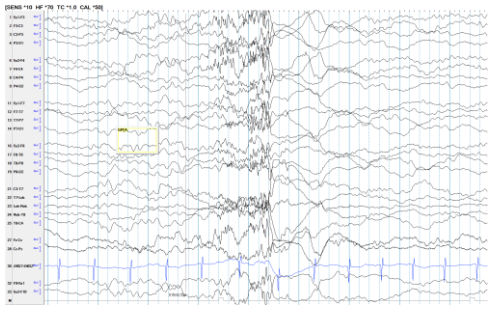
## LGS: THE EEG

- Varying degrees of diffuse slowing in 70% to 90%
- Slow spike wave commonly between 1.5 to 2.5 Hz (1 to 4 Hz)
- Characteristically irregular in frequency, amplitude, morphology, distribution
- Paroxysmal fast activity, 10-20 Hz, higher amplitude frontally, 5 to 10 seconds

## SSW



## GPFA



## LGS: TREATMENT

- Characteristically drug resistant
- Valproate
- Felbamate, topiramate, lamotrigine
- Clobazam, rufinamide
- Ethosuximide, levetiracetam, zonisamide
- Vagus nerve stimulation, corpus callosotomy

## LGS: LONG TERM OUTCOME

- Medically refractory epilepsy, neurocognitive deficits, episodes of status epilepticus, institutional care
- Slow spike waves persist in more than 1/3, focal spikes (esp. multifocal spikes) in 1/3
- Poor prognostic factors
- Symptomatic LGS (esp. if preceded by West syndrome)
- Onset less than 3 years of age
- High frequency of seizures and repeated episodes of status epilepticus
- Persistence of diffuse slow spike wave

## CONTINUOUS SPIKE AND WAVE DURING SLEEP (CSWS) AND LANDAU KLEFNER SYNDROME (LKS)

- Classified as epileptic encephalopathies.
  ILAE Task Force, 2001
- Age related focal epilepsies, self limited
- Seizures occur to variable degree in active phase of illness
- Linguistic, cognitive and behavioral disturbance

## LANDAU-KLEFFNER SYNDROME (LKS)

- Age of onset 3 to 8 years in a child who has already developed language
- Verbal auditory agnosia, disrupted speech, paraphasias, phonological errors, mutism
- Seizures generally run a benign course, subside by 15 years of age

## LANDAU-KLEFFNER SYNDROME (LKS)

- Bilateral temporal (mainly posterior temporal) epileptiform discharges
- Marked activation in slow wave sleep
- Disappear or fragment in active sleep

## CONTINUOUS SPIKE AND WAVE DURING SLEEP

- May evolve from atypical benign childhood epilepsy with centro-temporal spikes (4 to 6 years)
- Begins in childhood, remits in adolescence usually before puberty
- First seizure typically nocturnal and unilateral
- Focal motor seizures, absences, generalized tonic clonic
- Never tonic seizures!!!

## CONTINUOUS SPIKE AND WAVE DURING SLOW WAVE SLEEP

- Behavioral, attentional and cognitive symptoms predominate
- Focal and bilaterally synchronous spike wave discharges over the anterior hemisphere and generalized spike wave (1.5 to 3 Hz) while awake; spike wave index 25%
- Continuous generalized spike wave (1 to 3 Hz) in slow wave sleep; spike wave index > 85%
- Paroxysmal fast activity does not occur

## LKS AND CSWS: TREATMENT

- No controlled trials of treatment efficacy
- Corticosteroid therapy or ACTH may have favorable and long lasting effects
- Benzodiazepines
- Multiple subpial transection
- Goal is the complete elimination of the paroxysmal activity, preferably within the first 2 years, to prevent serious neuropsychological sequelae

## LKS-CSWS: LONG TERM PROGNOSIS

- <20% have persistent, rare seizures
- Those with earliest onset of spike and wave discharges and longer persistence of activity – the worst neuropsychological outcome
- LKS; some form of aphasia persist, only 50% able to live a normal life
- CSWS: complete restoration of function especially in verbal ability and attention is rare
- Persistent sequelae include short attention span, hyperactivity, affective symptoms and intellectual impairment

## Summary

- Can all epilepsies be associated with encephalopathy?
- Is etiology the main determinant of outcome (sodium channelopathy, glucose transporter deficit) ?
- To what degree do ongoing seizures and epileptic activity worsen the clinical picture?
- "…and these can worsen with time"
- How do we intervene?