Objectives

- Describe ESES and its impact on patients
- Identify therapies that may be used in the treatment of ESES
- Share preliminary data from ESES study being performed at Children’s Hospital of Wisconsin

Disclosures

- Learners must fill out and turn in evaluations to successfully complete this program.
- WNA CEAP or ANCC does not endorse any products within this presentation/program.
- There are no relevant financial relationships related to this presentation/program.
- There is no sponsorship/commercial support of this presentation/program.
- Off-label drug use will be discussed in this presentation.
- The content being presented will be fair, well-balanced and evidence-based.

LKS Syndrome

- Seminal case at Central Institute for the Deaf in St Louis
  - Acquired language normally then developed aphasia – primarily receptive; IQ – normal to above normal
  - Children also had epilepsy
  - Onset of aphasia over 1 day – several months; ages 4-8 years
  - EEGs –
    - generalized dysrhythmia with temporal predominance (3)
    - left temporal slowing (1)
    - isolated to right hemisphere (1)
  - Seizure types: convulsive, R focal motor, myoclonic, absence
  - Outcome
    - Seizures readily improved with AED (or no) therapy
    - Aphasia improved with AED c/r ST (or no therapy)
    - Aphasia improvement correlated with EEG improvement
    - Duration of aphasia 2 wks – several years

LKS – 50 years later

- Acquired aphasia –
  - verbal agnosia followed by expressive aphasia and decrease in spontaneous speech
  - Infrequent seizures – easy to control
  - Onset 2-8y, peak 5-7y, range 18m-14y
  - Boys twice as common as girls
  - EEG:
    - Wake – bilateral C, T, posterior 1 or P-O S/W
    - Sleep – continuous diffuse S/W discharges
    - BECTS – most common finding before acquired aphasia
  - Seizure types: focal motor, atypical absence, hemiconic, GTC, atonic
  - Outcome
    - EEG correlates with language impairment
    - EEG abnormalities longer than 3 years = long-term deficits

Landau & Kleffner, 1957

Caraballo et al, 2014; Dutta et al, 2013; Rudolf et al 2009
**LKS vs. ESES/CSWS**

- **LKS** – clinical syndrome
- **ESES** (electrical status epilepticus of slow wave sleep) – 1st reported in 1971
  - electrographic pattern
  - wider range of cognitive impairments
- **CSWS** (continuous spike and wave in slow wave sleep) – adopted by ILAE in 1989
  - used to describe EEG pattern without regard for seizure
- “Two syndromes (LKS, ESES) are distinct but have some overlap” (McVicar & Shinnar)

**Spectrum?**

- 40-50% of LKS patients develop ESES
- 40% of patients with verbal auditory aphasia have ESES
- 70-100% of LKS patients with behavior disorders had frontal & temporal discharges
- Earlier onset or longer duration of ESES
  - Global regression of cognitive/behavioral function may occur

**BECTS on Spectrum**

- BECTS characterized by increase in central discharges during sleep
- ESES may develop secondary to increase discharge rates and longer duration of CSWS
- Aicardi – 25 yr ago
  - syndrome resembling BECTS with atypical features – frequent brief seizures, atypical absence, focal positive or negative myoclonia
  - cognitive impairment
  - CSWS on EEG
- Contributing factors to development of ESES
  - atypical signs/symptoms
  - high discharge rates
  - neuropsychiatric/cognitive dysfunction
  - lack of response to AEDs
  - pre-existing neurologic condition

**ESES**

- Incidence – 1% of children with epilepsy
- CSWS pattern resolves by mid-teens
- Regression
  - Language – acquired aphasia, receptive followed by motor aphasia
  - Cognitive – memory impairment
  - Behavioral
  - Motor – ataxia, apraxia, dystonia, unilateral – e.g. hemiparesis

**Types of ESES**

- **Symptomatic**
  - Structural lesions
  - Seizures – hemiclonic, 2nd GTC, focal motor/automatisms
  - EEG – continuous regional or diffuse
  - Cognitive dysfunction - marked
- **Idiopathic**
  - Early normal development
  - Seizures – “atonic”, atypical absence, drop
  - EEG – diffuse
  - Cognitive dysfunction - some

**EEG with ESES**

- **Awake EEG**
  - Focal frontal or generalized
  - Bitemporal discharges
  - Minimal abnormalities during wave
- **Sleep EEG**
  - Nearly continuous, irregular generalized spike-wave complexes – Hallmark
  - At least 85% of sleep record
- Discharges are believed to result from secondary bisynchrony with corpus callosum likely playing important role
Pathophysiology

- Comorbid conditions – hydrocephalus, schizencephaly, prenatal bleed, CP
- Anatomy – thalamic lesion, limbic system, corpus callosum
- Hypotheses
  - Landau & Kleffner – functional ablation of eloquent cortex by frequent discharges
  - Increased glucose metabolism at epileptic focus leads to hypometabolism in other areas causing neuropsychological regression
  - Autoimmune process based on response to steroids?

Evaluation of ESES

- History
- Video EEG monitoring
- Optional
  - MRI – lesions found – 20% - classic lesions seen in CP & perinatal injuries
  - Genetics – CSWS seen in known chromosomal anomalies – e.g. 15q region, Rett syndrome
  - GRIN2A mutation – recently associated with some patients with epileptic encephalopathies
  - PET or MEG – if specific question such as epilepsy surgery

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Treatment

- Antiepileptic medications
- Immune modulation
- Ketogenic diet
- Surgery

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Surgical Interventions

- Multiple subpial transections
  - Has been used in small series of pts with LKS
  - Recent series (Downes et al) comparing MST (n=14) with non-surgical tx (n=21) found no differences in language, non-verbal ability, adaptive behavior, QOL
  - Epilepsy surgery that terminates szs and CSWS may have positive developmental outcomes

Treatment

- Immune modulation
  - Steroids –
    - Used in combo with AEDS – suppress EEG activity, improve cognition and social skills, slower improvement in language
    - 44 pts treated with hydrocortisone (5 mkd, maintenance 2 mkd) for 1 yr – 75% responded in 3 months, 50% normalization of EEG, 45.4% relapse, response associated with higher IQ and shorter duration of CSWS pattern
  - IVIG –
    - Improvement in 3 out of 9 patients
    - Neurocognitive improvement in 1 out of 3 patients

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Treatment Outcomes

- 112 articles with 950 treatments in 575 patients
- Best outcomes with surgical intervention (90%), steroids (80%), and benzodiazepines (68%)
- Consecutive assessments demonstrated less sustained outcomes, except surgical outcomes (which improved long-term)

van den Munckhof et al, 2015

Outcome

- Treatment outcomes:
  - 50% - drug treatment ineffective
  - ESM + VPA effective in 30% (add Inutska results)
  - Efficacy of LEV varied from 0-50% - may be more effective if classic LKS
  - Steroids varied from effective to no response
  - Spontaneous resolution of CSWS despite drug treatment choice with adolescence
  - Surgical outcome – see Peltola et al
- 32% good cognitive outcome
  - 90% EEG responders

Liukkonen et al, 2010; Inutska et al, 2006

Focal ESES

- Argentina series – n=21
- Anatomy – unilateral polymicrogyria (11), shunted hydrocephalus (4), porencephalic cyst with PMG (3), thalamic lesion (3)
- Median age of onset – 6 yrs
- Duration – 6-36 months
- Seizures
  - Focal c/s 2° GTC
  - With onset of hemi-ESES – change in sz type:
    • Drop, myoclonic, absence

Fortini et al, 2013

EEG – Focal ESES

- Baseline
  - 70.5% focal, 43% multifocal, 14.5% focal with generalized paroxysms
  - Focal spikes increase with sleep
- Hemi-ESES awake
  - Interictal increased – focal, multifocal, isolated
- Hemi-ESES sleep
  - 43% focal, 19% bilateral, 24% both focal and diffuse

Fortini, 2013

Regression – Focal ESES

- Motor impairment (negative myoclonus) – 67%
- Deterioration in baseline cognitive status – 76.2%
- Attention – 33.5%
- Language (non-verbal agnosia) – 24%
- Aggression – 28.4%
- Memory deficit – 19%
- Impaired temporospatial orientation – 19%
- Urinary incontinence – 14.3%

Fortini, 2013

Outcomes – Focal ESES

- Worsened electroclinical status
  - OCB, LTG, TPM, PB, PRM, CBZ
- Positive response – combinations of
  - Clobazam, ESM, sulthiame, VPA, steroids, KGD
- Surgery – hemispherectomy (2), partial lesionectomy (1)
- 33% did not respond to AEDs
- All AED responders [sz free or > 75% reduction in sz] returned to baseline cognitive development
- Best outcome – unilateral lesion

Fortini, 2013
Long-term Outcomes

- 13-year follow-up (n=117)
  - Symptomatic (n=79), idiopathic (n=38)
  - 79% of idiopathic group remained sz-free
  - 40% had focal spikes
  - 19% of symptomatic group sz-free; 57% - sporadic szs; 7.6% poor sz control
- EEG – focal, multifocal, bilateral asymmetric spikes
- Outcome dependent on etiology
  - Idiopathic – best outcome
  - Polymicrogyria – most CSWS resolved, only sporadic sz
- Cognitive outcome
  - Sz free or >75% reduction – significant improvement in IQ and school performance
  - 30% persistent cognitive regression – most symptomatic type

References