CATASTROPHIC EPILEPSIES OF CHILDHOOD

EPILEPTIC ENCEPHALOPATHIES

Childhood Epilepsy Syndromes

- Epilepsy Syndrome
  - Grouping of similar epileptic patterns according to seizure type, EEG, age of onset, family history, prognosis, response to treatment
- May categorize by developmental outcome
  - Benign
  - Intermediate
  - Catastrophic

Catastrophic Epilepsies of Childhood

- Neonatal
  - Early Myoclonic Encephalopathy
  - Early Infantile Epileptic Encephalopathy (Ohtahara syndrome)
  - Severe Myoclonic Epilepsy of Infancy (Dravet syndrome)
  - Infantile Spasms (West syndrome)
  - Malignant Epilepsy with Migrating Partial S"s
  - Lennox-Gastaut syndrome
  - Myoclonic-astatic epilepsy (Doose syndrome)
  - Landau-Kleffner syndrome
  - Epilepsy with Continuous Spikes-Waves during Slow Sleep
- Infantile
- Childhood

Epileptic Encephalopathies

- ILAE Definition
  - A condition where the epileptiform abnormalities themselves are believed to contribute to a progressive disturbance in cerebral function
  - Diffuse brain dysfunction is caused, at least in part, by some aspect of the epilepsy itself
  - Intractable seizures and severe cognitive dysfunction typical

Today’s Discussion

- Early Infantile Epileptic Encephalopathy (Ohtahara Syndrome)
- Infantile Spasms (West Syndrome)
- Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome)

Severe Myoclonic Epilepsy of Infancy (Dravet syndrome)
Severe Myoclonic Epilepsy of Infancy (Dravet syndrome)

- Typical onset 3-12 mos in previously normal child
- Recurrent febrile seizures in first year of life in 71%
  - Generalized > unilateral, and clonic
- Less frequent other seizure types early:
  - Myoclonic, generalized tonic-clonic, or afebrile seizures
- Status epilepticus common
- Regression occurs as early or late as the 3rd year of life

- Secondary seizures from 1 to 4 years of age:
  - Seizures become longer and afebrile
  - Myoclonic seizures, generalized or focal
  - Generalized tonic-clonic seizures
  - Partial seizures (50-75%) (hemiclonic, SM, CPS)
  - Atypical absences (40%)
  - Non-convulsive status epilepticus common
  - Generalized tonic seizures less common

- Interictal EEG normal initially
  - Later evolution of multifocal spike discharges, generalized slowing
- Ictal EEG depends on seizure type
  - Generalized spike, poly-spike & wave discharges during myoclonic seizures
  - Photosensitivity may occur in 1st year (64% overall)

- Etiology
  - 70-80% w/ various mutation(s) in α1 subunit of SCN1A
  - Most cases are de novo
  - Most introduce a premature stop codon, resulting in truncation and loss of protein function
  - Poor phenotype-genotype correlation
  - Rare PCDH19 mutation in some female patients, GABRA1, SCN2A, SCN1B, GABRG2 mutations also reported
Severe Myoclonic Epilepsy of Infancy (Dravet syndrome)

- Poor response to treatment
  - Valproate, levetiracetam, clobazam/benzos, topiramate, zonisamide, ethosuximide, felbamate, stiripentol
  - Ketogenic diet (up to >50% sz decr in DS)
  - May aggravate seizures: carbamazepine, phenytoin, lamotrigine, lacosamide, rufinamide, vigabatrin
  - Stiripentol w/ VPA and clobazam efficacious in 1 randomized controlled trial

- Poor prognosis – Up to 50% with IQ <50
- Rare cases reported with only mild delays
- Ataxia (60%), pyramidal signs (20%), & interictal myoclonus (36-85%)
- Lifelong epilepsy, myoclonic seizures resolve
- 5-15% mortality (status epilepticus & SUDEP)

Infantile Spasms (West syndrome)

- Onset before 12 mos in over 90% cases
- First described by Dr. W.J. West in his son, in a letter to the Lancet, 1841
  - Triad of West syndrome
    - Infantile spasms
    - Hypsarrhythmia
    - Developmental deterioration

- 60 – 70% symptomatic, rest idiopathic/cryptogenic
  - Structural/metabolic – HIE, stroke, PVL, hemorrhage, cerebral dysgenesis, PKU, NKH, B6 dependency
  - Genetic – Down, TSC, 1p36 del, STXBP1, ARX, CDKL5, SLC25A22, SPTAN1, PLCβ1, MAGI2, PNKP
Infantile Spasms (West syndrome)

- Sudden, brief flexor and/or extensor spasms
  - Often subtle and isolated at onset, then daily clustering later in course
  - Most prominent during drowsiness
  - Initial contraction phase followed by a more sustained tonic phase
  - May be asymmetrical

Hypsarrhythmia - classic interictal EEG pattern

- Disorganized background
- High voltage (>300 µV) slowing
- Frequent bursts multifocal spike/sharp waves
- Generalized electrodecremental ictal pattern
- Diffuse slow wave with electrodecrement, often with low amplitude paroxysmal beta activity

Treatment

- Corticosteroids first line
- Vigabatrin with tuberous sclerosis complex
- Other: KGD, levetiracetam, topiramate, valproate, zonisamide, benzodiazepines
- Epilepsy surgery if lesional, refractory

Evidence-based guideline update: Medical treatment of infantile spasms

ABSTRACT


Methods: MEDLINE and Google Scholar were searched from 2000 to 2013, and references of references of published articles were reviewed. Studies were included in the analysis. Recommendations were based on a graded classification scheme, including grade I evidence and level of evidence.

Results: Corticosteroids are the most effective treatment for infantile spasms, and vigabatrin is ineffective. Other agents, such as vigabatrin, topiramate, and benzodiazepines, show promise.

Adverse effects: Adverse effects are common with corticosteroids and vigabatrin. Other agents, such as levetiracetam and topiramate, may also cause side effects.

Conclusion: The evidence is insufficient to support the use of other agents in the treatment of infantile spasms. Further research is needed to identify the most effective treatment for this condition.
2012 IS Treatment Update

Vigabatrin (Sabril)
- US approval in 2009 for IS and add-on Tx for refractory partial epilepsy
- Black box warning for potential permanent visual impairment
- Dose and duration dependent retinal toxicity – lower risk with shorter term use
- Rare acute encephalopathy
- Rare lesions with restricted diffusion in deep nuclear, brainstem structures, reversible

Vigabatrin- Monitoring
- Lundbeck SHARE: Ophtho exams at baseline, q 3 mos on Tx, and 3-6 months after discontinuation
- Testing methods not specified
- Visual acuity and visual fields should be attempted
- ERG and VEP may be useful if limited cooperation
- MRI if encephalopathy or neurological dysfunction emerges

Infantile Spasms - Prognosis
- Early effective treatment may improve cognitive outcome
- Only 16% of all cases have normal development, 47% with seizures at 31 month f/u
- By etiology, normal development in 51% of cryptogenic vs only 6% of symptomatic cases
- Up to 60% will progress to other epilepsies
- About 17% will progress to LGS

Infantile Spasms (West syndrome)
- Recently concluded Canadian randomized, double-blind trial of add-on flunarizine to prevent cognitive deterioration associated with infantile spasms
- Ongoing International Collaborative Infantile Spasms Study (ICISS) – multicenter RCT comparing hormonal Tx + VGB, vs hormonal Tx alone
Lennox-Gastaut Syndrome

- Onset between 2-8 yrs, often before 5 yrs
- Etiology
  - 30% cryptogenic, 70% symptomatic
  - Up to 1/3 of cases occur in previously normal children
  - Cerebral malformations, HIE, encephalitis common
- Development slowing or arrest
- Early onset have greater intellectual impairment
- Behavioral problems in 50%

Lennox-Gastaut syndrome

- Mixed seizure disorder
- May begin with IS, evolving to multiple sz types
- Tonic seizures – brief, nocturnal, in 80-90%
- Atonic/drop attacks – risk for self injury
- Atypical absences – in 2/3 of cases
- Myoclonic, GTCS, Partial sz’s less prominent
- Frequent daily seizures
- Convulsive and non-convulsive SE common

Lennox-Gastaut syndrome

- EEG
  - Gen slow spw pattern (1.5-2.5 Hz)
  - Multifocal & generalized epileptiform discharges
  - Background slowing

Lennox-Gastaut syndrome

- Treatment difficult, drug resistant
- Valproate, lamotrigine, felbamate, topiramate, rufinamide, clobazam/benzos, lacosamide
- Palliative focal resection if lesional
- Drop attacks – corpus callosotomy, VNS
- Ketogenic diet
- Corticosteroids, IVIG

Clobazam (Onfi)

- Approved as adjunctive Tx for LGS ≥2 yrs of age
- RCT of 217 LGS subjects, adjunctive Tx of 5-40 mg/day for 12 weeks significantly decreased drop seizures, dose dependent
- Drop decrease by 58% in ≥50% of subjects in 1.0 mg/kg/d group
- Additional data: up to 91% reduction in drop szs to 24 months

Rufinamide (Banzel)

- Novel agent, triazole derivative, prolongs inactive state of Na channels
- Approved 2008 as adjunctive Tx for LGS for >4 yrs of age - drops
- QT shortening – consider EKG
- Reduces drops, myoclonic seizures
- RCT in 138 LGS patients > 12 yrs: mean sz frequency reduction by 32% RFN vs 11% placebo (goal 45 mg/kg/d), with 42% reduction in drops in RFN group

Lennox-Gastaut syndrome

- Poor Prognosis
- Intellectual disability up to 100%
- Seizures may improve over time, but persist
- Cognitive outcome parallels seizure frequency
- Slow spike and wave tends to resolve
- Early onset IS, lesional cases, repeated status associated with poorer outcome
- Increased mortality risk

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