Initial Treatment of Seizures in Childhood

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Incidence of Seizures

Overall 5% by age 20 yrs.

Lifetime risk= 5-10%

CNS Infections= 5%

TBI=10%

Incidence of epilepsy

- Bimodal peak of epilepsy
  - Infancy and childhood, elderly
  - Lifetime risk 3-5%
  - Prevalence 1%

To treat or to wait on therapy

- *Straightforward to wait*
  - Rare febrile seizures
  - Syncopal convulsions
  - First time unprovoked seizure

To treat or to wait on therapy

- *Complex decision making*
  - Recurrent benign seizures (e.g., Benign Rolandic, infrequent absence, complex febrile)
  - Second seizure
  - First seizure with a know abnormal EEG or a condition with increased risk (CP, tumor, old injury)

To treat or to wait on therapy

- *Straight forward to threat*
  - Threatening presentations (status epilepticus)
  - Serious co-morbidities; infection, stroke, tumor, trauma with hemorrhage

Treatment Options

- Treatment is tied directly to:
  - Underlying cause
  - Risk/benefit of medications
    - Side effects
    - Recurrence risk
    - Safety, compliance, access to care
    - Incomplete safety and efficacy data in childhood

Classification of Seizures-Generalized

- Absence
- Myoclonic
- Tonic
- Clonic
- Tonic-clonic
- Atonic

Classification II

- 2. Partial/Focal
  - Simple
  - Complex
  - With secondary generalization

Classification III

- Unclassified seizures
  - Febrile
  - Neonatal
  - Reflex
  - Nonepileptic
  - Acquired Aphasia

General Approaches to seizures

- No treatment for first seizure
- Hx, PE, directed further evaluation.
- EEG any first afebrile seizure.
- Imaging of brain in selected situations
- Treat for 2nd, or 3rd seizure: excepting status, febrile seizures.
- Initial drug-
  - Infant—Phenobarbital
  - Child/toddler– levetiracetam or Tegretol/Trileptal if EEG normal. VPA, levetiracetam, Lamictal or Zonegran if spike and wave.
  - Diastat for first aid

Status epilepticus—in the field

- Supportive (airway, glucose, etc.)
- Use of benzodiazepines, rectal valium (Diastat) up to 0.6 mg/ kg, up to 20 mg size. Some caution in children under 2 yrs old at high doses.
- Intravenous diazepam or lorazepam

Status epilepticus in hospital

Stop seizures!

- Benzodiazepines
  - Ativan 0.1mg/kg
  - Phenobarbital 20 mg/kg
  - Fosphenytoin 20 mg/kg (PE)
  - May repeat either phenobarbital or phenytoin 10 mg/kg

  (IV levetiracetem may replace phenobarbital)

- Hx,PE,Labs(Lytes,Ca,Mg,Glucose, tox),
- Imaging, EEG

Refractory Status (>60 min)

- Grave situation
- Requires specialized ICU care

Neonatal seizures

- Etiology usually clear or strongly suspect
- HIE
- Subarachnoid hemorrhage
- Drug withdrawal-opiates, SSRIs
- Infection
- Stroke, venous thrombosis
- Severe electrolyte disturbance
- Metabolic-Urea cycle, glycine encephalopathy, pyrodoxine dependency, proprionic, methylmalonic, Mo cofactor deficiency, etc.
- Benign familial neonatal epilepsy

Neonatal seizures

- Multiple types: focal, tonic, clonic, multifocal, subtle.
- Clinical: grimace, focal change in tone, clonic movements,bicycle, lip-smacking ,eye deviation.
- Apnea is a unique and threatening form of seizure in term infants.

Treatment

- Treating the underlying problems may be critical to outcome.
- Increasing evidence for seizures contributing to outcome.
- Unique problem of life-threatening apnea with seizures of even a benign cause.

Evaluation

- Hx,PE,Labs(Lytes,Ca,Mg,Glucose) ,imaging, EEG
- Stop seizure-
  - Benzodiazepines
    - Ativan 0.1mg/kg (NO DIAZEPAM)
    - Phenobarbital 20mg/kg
    - Fosphenytoin 20 mg/kg (PE)
    - May repeat either phenobarbitol or phenytoin 10 mg/kg

Additional AEDs?

- Increasing movement of very aggressive seizure management
- Special cases-Pyridoxine and other metabolic disorders
- Keppra and Zonegran, Topamax also in use. Tegretol/Trileptal is occasionally used requiring high doses of meds. All these are off-label, but widely used measures.

Prognosis

- Determined by underlying cause
- Infant with normal exam has 90% chance of no further seizures, and normal development.
- Even in infants with significant issues, stroke, HIE therapy may be short term-weeks to months depending on local approaches

Febrile seizures

- Most common cause of childhood epilepsy—linked to 2 major Na^+ channel mutations. Usually occurs later than 3 months and ends by 4 years.
- Many other seizure types may be activated by fever.
- History (with family history), exam, routine laboratory, consideration of cause of fever, and presence of a normal intericatal EEG are diagnostic. Gene testing is available, but not recommended.

Treatment of febrile seizures

- If seizure is prolonged, can treat as any case of status epilepticus with a higher preference for phenobarbital.
- Phenobarbital (and valproate) can reduce risk of recurrence but are not recommended except in rare situations.
- Rectal valium has been the treatment standard

Febrile Status epilepticus

- Usually occurs early in the course of febrile seizures and can be focal.
- Most common cause of status epilepticus with an unusually favorable prognosis for this diagnosis.
- Most studies are moving away from daily preventive seizure medications.

Syncopal convulsions

- Common with breath holding spells.
- Relatively common in adolescence and adult life.
- Rarely associated with long seizures, and treatment-resistant at all ages.

Absence vs Daydreamer

Absence

-3-12 yrs.

Peak 6-8 yrs.

Girls >Boys

A few to Hundreds a day

Interrupts speech, activity

Hyperventilation provokes absence

GTC 40%

Remit usually 10-11

10% refractory

Daydreaming, ADD

Same age

Boredom

Less frequent

Longer duration

Will not interrupt

Hyperventilation will not provoke

Many children with absence also have ADD

Treating Absence

- Ethosuximide vs. Valproate
- Ethosximide and valproate are used at 10-40 mg/kg divided bid to tid. Use extended release form of valproate if possible.
- Both require monitoring laboratories
- Carbamazepine, oxcarbazepine, phenytoin contraindicated

Treatment refractory absence

- 10-15% of cases.
- Higher risk in younger (3-4 yr old) or older (>10 yr)
- Often require multiple medications in combination. Little science to support choices.
- Keppra, Zonegran, Topiramate are possible adjunctive agents. No proof of effectiveness.

Special forms of absence

- For atypical cases (Juvenile absence or adolescent females, Lamotrigine is usually preferred (3-6 mg/kg divided bid)
- “Spike wave stupor” rare presentation of a “stuck” absence seizure—benzodiazepine or valproate effective

Benign Rolandic seizures

- Responsive to gabapentin, topiramate, lamotrigine, levetiracetam, oxcarbazepine. Oxcarbazepine is probably drug of choice, if decision to treat is made.
- Expanding number of nocturnal seizure syndromes, but most are variants of Rolandic seizures.

Benign Rolandic Seizures + other localization epilepsies

- Carbamazepine/ oxcarbazepine
- Important exception-nocturnal seizures with occipital spikes do best with valproate.
- Nocturnal symptomatic complex partial seizures are common
- A variety of less common focal seizures occur.

Juvenile Myoclonic Epilepsy

- Common generalized epilepsy-10% childhood
- GTC anytime, may precede other finding which is
- Myoclonus upon awakening-mistaken for clumsiness, tremor or shakes.
- Onset 12-18 yrs.
- EEG with polyspike and wave 4-6 Hz. (1/3 normal EEG, 1/3 3 Hz spike and wave)
- Atypical absence 30%
- Myoclonus is exacerbated by sleep deprivation, EtOH.
- Life long disorder (women often outgrow in 20's)

Treatment of JME

- Issues of polycystic ovary disease and significant weight gain with VPA.
- Many advocate lamotrigine as first line agent with consideration of zonisamide, levetiracetam
- Increasing focus on life-style modification.

Myoclonic Epilepsies

- Includes brief myoclonic seizures with “drop attacks”
- Often associated with developmental delay
- Treatment involves specialized decision making, but benzodiazepines or valproate can be used.
- Best to collaborate with neurology in decision making.

Infantile Spasm

- Initial treatment consist entirely of correctly recognizing the condition.

Infantile spasm

- 4-8 months
- 90% present by one year of age
- Characterized by seizure type, age of onset, EEG (hypsarrhythmia)
- Flexion, extension or both
- 40% no cause found (cryptogenic)
- Recognition of motor behavior is role of initial treatment. W/U and treatment is specialized.
- Primary care has a special role in supporting treatments.
- Treat-ACTH, vigabatrin

Treatment of infantile spasm

- Vigabatrin not yet FDA-approved (on Fast-track)
- Usual dose is 80-100 mg/kg/day

- 10-30% risk of visual field restriction.

Treatment of infantile spasms

- Consensus that ACTH should be attempted in all other cases.
- Debate on dose remains unresolved, but higher doses and shorter duration is the present trend.
- Cost is a major issue >$10,000-30,000/wk

Discontinuing meds.

- Risk of recurrence-
  - Overall 30-50%
  - Risk factors-
    - EEG findings
      - 27% if normal
      - 44% if abnormal
    - Etiology
      - Symptomatic(known cause-HIE, trauma, etc.) - 68%
      - Idiopathic- - 37%

Recurrence

- Recurrence
  - Sleep state with seizure
    - Asleep-53%
    - Waking-36%

Recurrence,etc..

- NOT predictive of recurrence:
  - Duration of seizure
  - Family Hx
  - Status Epilepticus, but recurrence may be prolonged if occurs.
  - ?Treatment
  - Age?, less than 2, focal motor.

Withdrawal of Medication

- 2 years seizure-free in US (Europe after 1 year).
- Risk of recurrence-25 to 40%
- Most recur within 6 mos. 80% by one year.
- Increased risk?
  - Abnormal exam, EEG
  - Increasing age of onset.
  - ? Seizure type

Young women and Epilepsy

- Teratogenic effects of Valproate- (need for high dose folate)
- Teratogenic effects of new generation drugs is unknown, but appear favorable.
- Issues of effects on oral contraceptive agents—
- Issues of bone demineralization

- “It is vain to do with more what can be done with fewer.

  --William of Occam

Appendix

- Specific drugs follow in a set of slides describing some specifics of dose.
- Slides that follow are included for reference

“New” treatment options

- Useful reformulation and derivative of medications
- “New” agents
  - Lamictal (lamotrigine)
  - Topamax (topiramate)
  - Zonegran (zonisamide)
  - Keppra (levetiracetem)
  - Gabitril (tiagabine)
  - Trileptal (oxcarbazepine)

Topamax (topiramate)
Zonegran (zonisamide)

- Broadly effective, can be used in young children according to experience.
- Side-effects similar; related to carbonic anhydrase effects; renal caculi, narrow angle glaucoma, poor tolerance of high temperature.
- Topamx has special cognitive concerns.
- Zonegran has some sulfa like structural characteristics.
- Probable bone demineraliztion—risk for virtually all anticonvulsants.

Dosage and formulation

- Topamax and Zonegran: available as sprinkle caps
- Topamax: dosing 2-8mg/kg/day
- Zonegran: water soluble and stable
  - 7-20 mg/kg/day—once a day dosing possible

Trileptal

- Dosing is 50-200% greater than Tegretol.
- Available as liquid
- Usually a single set of electrolytes obtained 2-3 months after starting

Trileptal (oxcarbazepine)

- Activated form of carbamazepine—avoids hepatic and bone marrow effects.
- Still can change renal H_20 clearance and produce hyponatremia—mostly an issue of hot climates and athletics.
- Must request specific levels
- Bone demineralization; probably better than carbamazepine
- Improvement for Alaskan patients because of drug monitoring.
- Note much higher dosing recommendations since release.

Keppra (levetiracetem)

- Broadly effective.
- Few serious side-effects, no need for blood monitoring.
- May cause severe agitation in some youngsters
- Commonly used in combination with Zonegran for myoclonic seizures.
- Effective in partial seizures
- Extensive use outside of approved ages
- Recent evidence suggest role in tic disorders—not approved or confirmed

Adjunctive therapies in refractory seizures

- Evaluation for epilepsy surgery
- Ketogenic diet—
- Vagal nerve stimulator-- Adjustments can be made by any local provider.