Childhood Epilepsy and Comorbidities

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4-year-old referred to you for poor seizure control

She has tuberous sclerosis and has been refractory to many AEDs

Frequent reasons for failure are behavior, sleep, and near-psychotic activity

The family also wants to know what school is best, and what is your strategy for repeat imaging

The comorbidities exceed the time available for the first appointment
Comorbidities in Epilepsy Patients: Physician Perceptions*

- Comorbidity in at least 20% of children/adolescents with epilepsy
  - Behavioral abnormalities
  - Impaired attention
  - Concurrent psychiatric disorder or learning disability
- At least 10% of children/adolescents with epilepsy have symptoms of depression

*Survey findings, CNS 2004
Comorbidity with Epilepsy

- Psychiatric disorders
- Migraine
- Reproductive dysfunction
- Accidents
- Osteoporosis
- Stroke, CVD, brain tumors
- Alzheimer’s disease in people aged ≥65 yrs
Pediatric Epilepsy: Common Comorbidities

- Cerebral palsy
- Mental retardation
- Congenital malformations
- Chromosomal abnormalities
- Genetic/metabolic disorders
- Prenatal or perinatal insults
- Psychiatric disorders
15%-38% of childhood-onset epilepsy associated with MR/cerebral palsy

Epilepsy is a common comorbid condition with developmental delay

Degree of disability correlates with higher incidence

Cause of symptomatic epilepsy and MR frequently the same

Approximately (or ≥) 50% of institutionalized patients with I/DD have active epilepsy
Epilepsy and Developmental Disabilities

- Incidence of epilepsy significantly greater among individuals with developmental disabilities
  - Chronic seizures occur in 30%-50% vs. ~1% in general population
    - Incidence of seizures increases with severity of developmental involvement
  - Cumulative incidence of epilepsy is >50% before age 5 yrs for those with multiple disabilities
# Seizure Types in Children Referred to Child Development Center

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>All Children (N=1,946)</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MR (N=264)</td>
<td>CP (N=35)</td>
</tr>
<tr>
<td>Generalized seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonic-clonic</td>
<td>40</td>
<td>19</td>
</tr>
<tr>
<td>Tonic</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Atypical absence</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Atonic</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Partial seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple partial</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Complex partial</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Secondarily generalized</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;1 seizure type</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>32</td>
</tr>
</tbody>
</table>

Treatment of Epilepsy Patients with Multiple Handicaps

- Achieve optimal control and functioning
  - Avoid agents that produce cognitive effects, if possible
  - Simplify AED regimen, avoiding polypharmacy if possible
  - Use most helpful, least aggravating AED
  - Avoid benzodiazepines and barbiturates
- Antidepressants
- Stimulants for attention deficits
- Behavioral management

Epilepsy and Autism

- Autism incidence: 3.4/1000
- Autism associated with increased seizure risk
- Dependent on degree of MR and CP (8–>28%)

Yeargin-Allsopp, 2003
Shinnar, Pellock, 2002
## Risk Factors for Epilepsy in Children with Autism and Dysphasia

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Epilepsy (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autistic</td>
<td>Dysphasic</td>
</tr>
<tr>
<td>No motor deficit and not severe MR</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Motor deficit and not severe MR</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Severe MR and no motor deficit</td>
<td>25</td>
<td>++</td>
</tr>
<tr>
<td>Motor deficit and severe MR</td>
<td>42</td>
<td>++</td>
</tr>
</tbody>
</table>

Prevalence of Psychiatric and Behavioral Comorbidities

- Population-based, retrospective study
  - Incident cases of epilepsy (1980-1995)
  - Rochester, MN

- Prevalence
  - DSM-IV diagnosis: 51% (69/104)
  - Without mental retardation and/or pervasive developmental disorder: 40.4% (44/109)

- Children with newly diagnosed epilepsy frequently exhibit comorbid psychiatric or behavioral disorders

ADHD

- Attention and hyperactivity are the most common behavioral symptoms reported in children with epilepsy
  - Prevalence ranges from 8%-77% depending on diagnostic criteria and sampling
- 38% epilepsy patients had provisional diagnoses of ADHD, as measured by rating scales and CBCL
- Methylphenidate safe for use in pediatric epilepsy patients with comorbid ADHD

Dunn DW, Austin JK. Neurology 53(Suppl 2): S96-S100, 1999
# Prevalence of Psychiatric Disorders

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>11-60%</td>
<td>2-4%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>19-45%</td>
<td>2.5-6.5%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2-8%</td>
<td>0.5-0.7%</td>
</tr>
<tr>
<td>ADHD</td>
<td>10-39%</td>
<td>2-10%</td>
</tr>
</tbody>
</table>

Kanner AM. Epilepsia 44:3-8, 2003
Pellock JM. Neurol, 2004
**Prevalence of Manic Depressive Symptoms**

<table>
<thead>
<tr>
<th></th>
<th>General population</th>
<th>Asthma</th>
<th>Diabetes</th>
<th>Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>8.7%</td>
<td>16%</td>
<td>17%</td>
<td>29%*</td>
</tr>
<tr>
<td>Manic depressive symptoms</td>
<td>2.1%</td>
<td>3.9%</td>
<td>3%</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

*Prevalence for men and women was identical

Kanner AM. Epilepsia 44:3-8, 2003
Depression in Epilepsy is Under-Recognized and Under-Treated

Potential reasons for delayed therapy in depression

- Patients minimize psychiatric symptoms
- Symptomatology differs between patients with / without epilepsy
- Fail to inquire about psychiatric symptoms
- Considered normal adaptative response to epilepsy diagnosis
- Risk of antidepressant therapy to lower seizure threshold

Delay not related to depression severity

Kanner AM et al. Epilepsy Behav 1:100-105, 2000
Kanner AM et al. Epilepsy Behav 1:37-51, 2000
Epilepsy, AEDs and Suicidality (FDA Alert: January 2008)

- AEDS: suicidal thoughts/behavior risk: 0.43 vs. 0.22 (pbo)
  - Estimated 2.1/1000 more patients on AEDs vs. PBO
  - Not specific to single drug or class
- Recommendations: class warning
  - Balance risk for suicidality with clinical need for AED
  - Be aware of possibility of emergence or worsening of depression, suicidality, or unusual changes in behavior
  - Inform patients, their families, and caregivers of the potential; symptoms such as anxiety, agitation, hostility, mania, and hypomania may be precursors to emerging suicidality
- Suicide rate increased in epilepsy
- Suicide rate increased in adolescents
Epilepsy and Suicidality
Update and Recommendations

Is AED and/or psychiatric comorbidity the more important risk?

• Identify psychiatric disorders
  - Neurologists not expected to manage

• Most frequent associated risks:
  1) Current or past history of mood/anxiety disorder
  2) Family psych history of mood disorder, particularly suicidal behavior
  3) Past suicide attempts

• Document Assessment
  - ? Format
  - Referral

Kanner, Ep Currents, 2009
Willmore, Pellock, 2009
Arana, et al, NEJM 2010
Mula and Sander, Neurology 2010
Andersohn, et al, Neurology 2010
Aggression and Childhood Epilepsy

Prevalence
- Difficult to determine
- Oppositional defiant disorder/conduct disorder: 10-35%

Occurs with restraint during postictal confusion and with postictal psychosis

Association with underlying central nervous system damage
Impulsivity and Aggression

Cluster B Personality Disorders

Borderline Personality Disorders

Sexual Compulsions

Substance Use Disorder

PTSD

Impulse Control Disorders

Autism Spectrum Disorders

Developmental Disorders

Tourette’s/OCD

ADHD Spectrum

Bipolar Spectrum

Impulsive-Aggressive Spectrum

PTSD
Comorbidity of Bipolar Disorder and Developmental Disorders

- Mania in children with pervasive developmental disorder revisited
- 21% of PDD patients in a referred sample met criteria for mania – mostly with irritability

Management of Behavioral Problems: Impact of Seizure Control

- Individual and group therapy
  - Assessment for emotional based precipitants, instruction in relaxation techniques and self-control
    - Improved self-concept
    - Reduced seizure frequency

- Stimulants
  - Improvement in symptoms of ADHD
    - No seizure breakthrough in children seizure-free
    - Probably no increase in seizure number in those with active seizures
Management of Behavioral Problems: Impact of Seizure Control

- **Antidepressants**
  - Risk in triggering seizures
    - Significant increase: high-dose bupropion
    - Moderate increase: certain tricyclic antidepressants (clomipramine) and any tricyclic antidepressant at toxic serum concentrations
    - Low risk: SSRIs, trazodone, nefazodone
  - Inhibition of cytochrome P450 may lead to increased AED levels

- **Antipsychotics**
  - Risk in triggering seizures
    - Significant increase: clozapine, chlorpromazine
    - Moderate increase: thioridazine, olanzapine, quetiapine
    - Low risk: haloperidol, risperidone
Non-Pharmacologic Treatment: IQ Independent

- Structure
- Predictability
- Communication
- Social skills
- Identify meaning of dyscontrol
- Instruct caregivers to monitor and measure behavior in detail, time of day, proximity to transitions, etc.
Epilepsy Adverse Effects: Cognition and Behavior

- Most AEDs can influence cognitive function
- Monotherapy better than polypharmacy
- AEDs may amplify or ameliorate behavior
- AEDs may exacerbate certain seizure types
- Seizure frequency may significantly affect cognition/behavior transiently and permanently

Recent research findings:
- Epilepsy intractability not an independent risk factor for depression*
- No relationship between depression severity and seizure frequency*

Selected CNS-Related Comorbidities in Epilepsy: Impact on AED Selection

- Depression
- Anxiety
- Psychiatric Disorders
- Migraine
- Cognitive Disorders
- Developmental Disorders in Pediatrics

National Profile of Childhood Epilepsy

2007 Survey, 977 of 91,605 reported epilepsy/seizures

Epilepsy/seizure prevalence higher in lower income families

Children with epilepsy/seizures
- Depression (8 vs 2%)
- Anxiety (17 vs 3%)
- ADHD (23 vs 6%)
- Conduct problems (16 vs 3%)
- DD (51 vs 3%)
- ASD (16 vs 1%)
- Headache (14 vs 5%)

Epilepsy/seizure group poorer education, social outcome

Migraine and Epilepsy

- Both common in childhood
- Migraine and epilepsy, increased with other (3-7% with migraines have epilepsy)
- Migraine the borderline of epilepsy
- Paroxysmal EEGs in 20% migraineurs
- Channelopathies
  - Treatment with appropriate AED
AEDs Used in Migraine

- FDA indication for migraine
  - Valproate*
  - Topiramate*

- Other AEDs without an FDA migraine indication
  - Gabapentin*
  - Lamotrigine
  - Zonisamide
  - Levetiracetam
  - Pregabalin

*Double-blind, placebo-controlled studies
Injury in Persons with ID

- Risk of injury doubles in children with ID and maladaptive behaviors
- Epilepsy is an independent but significant risk factor
- Epilepsy increases the age-based fracture rate
  - 15% without epilepsy
  - 26% when epilepsy is comorbid

Mortality and Survival

- Mortality rates and mean survival is determined primarily by level of cognitive impairment.
- Mortality risk doubles with presence of epilepsy.
- Incidence of sudden death triples in persons with epilepsy:
  - 1.3 per 1000 person-yrs without epilepsy
  - 3.6 per 1000 person-yrs with epilepsy

Childhood Epilepsy Comorbidity

- Comorbidity is frequent in childhood epilepsy
- Condition may significantly affect epilepsy
- Epilepsy may affect co-morbid condition
- Treatments impact co-morbid conditions
- Optimal treatment should be designed to benefit both
ABSTRACT:

Objective: This large, prospective, community-based study characterized neuropsychological functioning and academic achievement at the time of the first recognized seizure and identified risk factors for cognitive deficits.

Methods: We compared 282 children (ages 6-14 years, IQ≥70) with a first recognized seizure to 147 healthy siblings on a battery of well-standardized and widely used neuropsychological and academic achievement tests and examined relationships with demographic and clinical variables.

Results: In this intellectually normal cohort, 27% with just one seizure and up to 40% of those with risk factors exhibited neuropsychological deficits at or near onset. Risk factors associated with neuropsychological deficits included multiple seizures (i.e., second unprovoked seizure; odds ratio [OR] = 1.96), use of antiepileptic drugs (OR = 2.27), symptomatic/cryptogenic etiology (OR 2.15), and epileptiform activity on the initial EEG (OR = 1.90); a child with all 4 risks is 3.00 times more likely than healthy siblings to experience neuropsychological deficits by the first clinic visit. Absence epilepsy carried increased odds for neuropsychological impairment (OR = 2.00).

Conclusions: A subgroup of intellectually normal children with seizures showed neuropsychological deficits at onset. Academic achievement was unaffected, suggesting that there is a window early in the disorder for intervention to ameliorate the impact on school performance. Therefore, the risk factors identified here (especially if multiple risks are present) warrant swift referral for neuropsychological evaluation early in the course of the condition.
QOL Issues Associated with Epilepsy

- Fewer epilepsy patients married or have children
- More epilepsy patients live at home with parents, in foster homes, or institutions
- Epilepsy at school age negatively affects learning, but no relationship between school achievement and epilepsy occurrence after age 18
- Seizures and AEDs associated with low self-esteem and social stigma
- Epilepsy patients consider their epilepsy separately from their general health
- Epilepsy patients underemployed