Correlation between epilepsy and attention deficit hyperactivity disorder

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Background
- Attention deficit/hyperactivity disorder (ADHD)
  A common neurodevelopmental disorder
- Significant effects on the social and behavioral development of children
- Severe and persistent symptoms, such as inattention, over-activity, and impulsiveness are associated with long-term educational and social disadvantages
- Frequent comorbidity with epilepsy

Epidemiology of ADHD among children with epilepsy
- ADHD affects about 3-5% of school age children, whereas the prevalence of epilepsy in children about 0.05%.
- ADHD in children with epilepsy: 12 to 39% in epidemiological studies
- Epidemiological studies demonstrated an increased incidence of behavioral problems of all kinds in children with epilepsy

Epidemiology of ADHD among children with epilepsy

<table>
<thead>
<tr>
<th>First Author, Year of Publication</th>
<th>Study Population</th>
<th>% With Hyperactivity or Combined</th>
<th>% With Inattention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutter, 1970 [4]</td>
<td>64 children with epilepsy</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>Holdsworth, 1974 [5]</td>
<td>85 children epilepsy</td>
<td>21%</td>
<td>42%</td>
</tr>
<tr>
<td>Bierwisch, 1990 [6]</td>
<td>43 children &lt;6 yr 60% intractable epilepsy</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Hoare, 1991 [7]</td>
<td>108 children with poorly controlled epilepsy, 5-15 yr</td>
<td>48% (54% parent rating scales)</td>
<td></td>
</tr>
<tr>
<td>Dunn, 2003 [8]</td>
<td>117 children with epilepsy for &gt; 6 mo, 9-14 yr</td>
<td>14%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Background
- 6.1% of ADHD abnormal EEG results; only 3.5% of healthy children (Pediatr Neurol, 2002).
- Children with unprovoked seizures: behavioral disturbances more common before the onset of the first seizure compared to controls (Pediatrics, 2001).
- 148 children with first unprovoked seizures and 89 seizure-free sibling controls: attention problems before the first seizure 2.4-fold more common in children with seizures (8.1%) than in controls (3.4%) (Seizure, 1997).
**Background**

- Most of the previous study regarding relationship between ADHD and epilepsy
  - Case control study (minority)
  - Review of medical records
  - Most studies have been undertaken in clinic settings and not in large populations

**Objective**

- Since there is a high association between ADHD and epilepsy, there might be a bidirectional relationship between these two disorders
- We performed a population-based cohort study to evaluate correlation between ADHD and epilepsy

**Data source**

- An electronic claims database of Taiwan National Health Insurance Research Database program (NHIRD)
  - covering 99% of the total 23 million population
  - contracting with more than 90% of health care facilities in Taiwan
- A subset of the longitudinal data containing randomly selected cohort of one-million insurants was used in this study

**Study design and subjects**

- Two cohort studies for evaluating the bidirectional relation between
  - attention-deficit hyperactivity disorder
  - ADHD: International Classification of Disease, Ninth Revision [ICD-9], Clinical Modification, code: 314.00, 314.01
  - epilepsy (ICD-9 345) using the same procedure to select study subjects.
- Study subjects were children under age 19 and without mentally retarded (ICD-9 317-319).
Results

Cohort 1: Epilepsy and Subsequent Risk of ADHD

- Prevalence for epilepsy: 0.34%
- The mean age was 8 years (SD ± 5.3 years) in epilepsy group, the same as the comparison group
- Male : Female = 1.2 : 1.0
- Distribution of the area : no significant difference

- The median follow-up – epilepsy group: 7.0 years – comparison group: 7.5 years

- The incidence of ADHD – Epilepsy: 7.76 per 1000 person-years (0.77%) – Comparison: 3.22 per 1000 person-years (0.32%)

Cohort 2: ADHD and Subsequent Risk of Epilepsy

- Prevalence for ADHD: 0.5%

- The mean age was 8.7 years (SD ± 3.0 years) in ADHD group, the same as the comparison group;
- Male : Female = 4 : 1
- Children living in higher urbanized area had higher percentage of ADHD (P <0.0001).

- The median follow-up – ADHD group: 3.3 years – comparison group: 3.5 years

- The incidence of epilepsy – ADHD group: 3.24 per 1000 person-years (0.32%) – comparison group: 0.78 per 1000 person-years (0.08%)

Table 2. Hazard ratios for incidence of ADHD with epilepsy

<table>
<thead>
<tr>
<th>Hazard ratio and 95% CI</th>
<th>Unadjusted</th>
<th>adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Patients with epilepsy vs. comparison group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2.52 (2.01-3.17)***</td>
<td>2.54 (2.02-3.38)***</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6</td>
<td>2.26 (1.74-2.93)***</td>
<td>2.26 (1.74-2.94)***</td>
</tr>
<tr>
<td>6-12</td>
<td>3.50 (2.13-5.74)***</td>
<td>3.53 (2.15-5.80)***</td>
</tr>
<tr>
<td>12-18</td>
<td>5.13 (1.38-19.69)*</td>
<td>5.30 (1.42-19.78)*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3.59 (2.19-5.86)***</td>
<td>3.59 (2.20-5.86)***</td>
</tr>
<tr>
<td>Male</td>
<td>2.31 (1.79-2.99)***</td>
<td>2.31 (1.78-2.98)***</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, urbanization level
PY: person-years at risk
"per1,000 person-years
"p<0.05, ""p<0.01, """"p<0.0001
Discussion

- ADHD and epilepsy: comorbid conditions. A bidirectional relationship between ADHD and epilepsy.
- In this study, ADHD increases the risk of subsequent epilepsy, and epilepsy increases the risk of subsequent ADHD.

<table>
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<th>Table 4. Hazard ratios for incidence of epilepsy with ADHD</th>
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<tr>
<td>Hazard ratio and 95% CI (Patients with ADHD vs. comparison group)</td>
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- Adjusted for age, sex, urbanization level
- PY: person-years at risk
- ¹per 1,000 person-years
- p<0.05, "p<0.01, ""p<0.001

Discussion

- The complex relationship between epilepsy and ADHD remains unclear.
- Possible pathophysiology of their comorbidity in the brain development:
  1. the effects of chronic seizures
  2. EEG epileptiform discharges
  3. antiepileptic drugs

Discussion

- Neurodevelopmental conditions: increase the vulnerability of children to epilepsy and ADHD.
- ADHD symptoms prior to the onset of seizures:
  1. Higher in children with epilepsy compared to their siblings 6 months prior to the first diagnosed seizure
  2. ADHD significantly more common in patients with new-onset epilepsy (31%) than in healthy controls (6%) (Am J Psychiatry 2005; J Child Neurol 2001).

Discussion

- This finding is consistent with the possibility of acquiring ADHD increases in epileptic children and independent of the effects of seizures or their treatment.
Discussion

- Frontostriatal network dysfunction:
  - A frontostriatal network dysfunction related to ADHD frontal lobe dysfunction appears in both focal-onset and generalized-onset types of epilepsy. *(Biol Psychiatry 2005)*

- Epilepsy-induced impairment of networks:
  - Seizure-induced rats simultaneously developed behavioral and physical characteristics similar to ADHD symptoms. *(Epilepsia 2007)*

Limitation of the Study

- Which type of ADHD had higher risk of developing epilepsy is unknown.
- Which type of epilepsy had higher risk of developing ADHD is unknown.
- Influence of AEDs/ADHD medication on subsequent seizure or inattention were not excluded.

Conclusion

- Early identification of ADHD and epilepsy comorbidity is crucial.
- Pediatric neurologists should look for temporal relationships between the course of the epilepsy, and the onset of ADHD.
- In children with epilepsy, might need ADHD treatment combination to improve long-term cognitive and behavioral prognosis.

Thank You for Your Attention