Correlation between epilepsy and attention deficit hyperactivity disorder: A population-based cohort study

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Correlation between Epilepsy and Attention Deficit Hyperactivity Disorder: A Population-Based Cohort Study

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Background

- Attention deficit/hyperactivity disorder (ADHD)
  A common brain disorder with onset in early childhood in widespread, but specific areas of the brain
- Frequent comorbidity with epilepsy
- Negative impact on their quality of life, significant risk factor for academic underachievement

Epidemiology of ADHD among children with epilepsy

- ADHD in children with epilepsy: 12 to 39% in epidemiological studies (3-5% in general population; in patients with epilepsy and overall normal IQ)
- Epidemiologic studies demonstrated an increased incidence in all kinds in children with epilepsy
- 52% had combined type, 35% inattentive type, and 13% hyperactive-impulsive type (Rhode, 1999)
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>Bravidor, 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>175 children with epilepsy for &gt; 6 mo, 9-14 yr</td>
<td>14%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Risk Factors for Inattention or ADHD in Children With Epilepsy

**Demographic factors**
- Gender: boys at increased risk—inconsistent
- Family history of ADHD—probable

**Neurologic variables**
- Learning disability or mental retardation
- Frontal lobe damage—possible association

**Seizure variables**
- Intractable seizures
- Frontal or temporal lobe focus—inconsistent
- Frequent subclinical discharges—possible

**AEDs**
- phenobarbital, benzodiazepines, topiramate, gabapentin
Background

Several factors may contribute to this comorbidity, including
- underlying brain pathology
- chronic effects of seizures and of the epileptiform EEG discharges,
- effects of antiepileptic drugs.
- psychosocial factors (environment)

Background

- **Neurodevelopmental disorders**: characterized by aberrant and delayed early-life development of the brain, leading to deficits in language, cognition, motor behaviour and other functional domains, often accompanied by somatic symptoms.

- **Environmental factors**: increase the risk of the heterogeneous, multifactorial and polygenic disorders.
Copy number variation in Tourette syndrome
Another case of neurodevelopmental generalist genes?

Neurology. 2010 May 18;74(20):1564-5.

Jeremiah M. Scharf, MD, PhD
Carol A. Mathews, MD

Despite decades of research demonstrating that Tourette syndrome (TS) has one of the highest familial recurrence rates among non-Mendelian neuro-psychiatric diseases, the search for the underlying genetic causes of TS has remained elusive. Examination in TS. Using a SNP-based genotyping platform, the authors analyzed CNV data in 111 patients with TS compared to 73 European ancestry controls. Since the distinctions between normal and pathogenic CNVs are still in flux and the various computational...
Genetics of neurodevelopmental disorders

- The same large (100 kb) deletions/duplications present in patients with a wide range of neurodevelopmental phenotypes
- Including autism, developmental disability, schizophrenia, attention deficit hyperactivity disorder (ADHD), and seizures
- An abnormality in one gene, perhaps acting in concert with other genetic or environmental factors, could manifest in many different phenotypes

The Genetics of Related Disorders

- Copy-number changes
  - schizophrenia
  - epilepsy
  - attention deficit–hyperactivity disorder (ADHD)
  - Autism
  - Intellectual disability
  - Tourette syndrome
Developmental neurobiology of ASD risk genes. (A) Diverse subcellular distribution and pleiotropic roles for syndromic and idiopathic ASD proteins. (B) Expression profiles of select previously established and newly identified ASD genes during development of the human neocortex. *Science Vol 337, Sep 2012*

**Many-to-one relationship**

- Gene-brain-behavior relationships
- Emergence of higher-order functions disrupted in psychiatric disorders influenced by neurodevelopmental processes guided by thousands of genes
- Organized circuitries that include sensory and motor, autonomic regulatory, social emotional and cognitive domains
- ASD has steadily increased, now reaching well into the hundreds, with no single locus accounting for more than 1% of cases.
- This suggests that future studies need to go beyond isolated molecular dissections of single mutations.
“One-to-many” phenomenon

- Overlap of risks for distinct disorders.
- Identical highly penetrant variants in different individuals carry large effects but for a wide range of outcomes, including, but likely not limited to, ASD, epilepsy, intellectual disability, and schizophrenia.
- This “one-to-many” phenomenon, combined with the biological pleiotropy of genes that have so far been implicated in ASD.

Spatio–temporal transcriptome of the human brain


Brain development and function depend on the precise regulation of gene expression. However, our understanding of the complexity and dynamics of the transcriptome of the human brain is incomplete. Here we report the generation and analysis of exon-level transcriptome and associated genotyping data, representing males and females of different ethnicities, from multiple brain regions and neocortical areas of developing and adult post-mortem human brains. We found that 86% of the genes analysed were expressed, and that 90% of these were differentially regulated at the whole-transcript or exon level across brain regions and/or time. The majority of these spatio–temporal differences were detected before birth, with subsequent increases in the similarity among regional transcriptomes. The transcriptome is organized into distinct co-expression networks, and shows sex-biased gene expression and exon usage. We also profiled trajectories of genes associated with neurobiological categories and diseases, and identified associations between single nucleotide polymorphisms and gene expression. This study provides a comprehensive data set on the human brain transcriptome and insights into the transcriptional foundations of human neurodevelopment.
1340 samples and 16 human brain regions, 15 developmental periods, ranging from embryonic development to late adulthood

Figure 2: Age at which tics and coexisting disorders affect patients. Width of bars shows schematically the amount the disorder affects a
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 were:
  - 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 the 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.

Epilepsy ..... ↑ADHD

ADHD.....↑ Epilepsy
**Data source**

- An electronically claims database of Taiwan National Health Insurance (NHI) program
  - 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**

- we conducted two analysis 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 in this study were children under age 18 and without mentally retarded (ICD-9 317-319).
In analysis 1, we selected children newly diagnosed epilepsy during 1999-2008 and a non-epilepsy comparison group, excluding those with ADHD before.

Analysis 2 contains children newly diagnosed ADHD during 1999-2008 and a non-ADHD comparison group, excluding those with epilepsy before.

Index date was defined as the date of diagnosis with epilepsy (analysis 1) or ADHD (analysis 2).

Comparison groups:
- randomly selected
- matched on exact age, sex and the index year
- based on a control-to-case ratio 4.

All patients were observed from the index date to the date of ADHD (analysis 1) or epilepsy (analysis 2), cancellation of insurance coverage, death or December 31, 2008, whichever came first.
Analysis 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
Analysis 1: epilepsy and subsequent risk of ADHD

- 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%)

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio and 95% CI</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(Patients with epilepsy vs. comparison group)</td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>All</td>
<td>2.52 (2.01-3.17)***</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>0-6</td>
<td>2.26 (1.74-2.93)***</td>
</tr>
<tr>
<td>6-12</td>
<td>3.50 (2.13-5.74)***</td>
</tr>
<tr>
<td>12-18</td>
<td>5.13 (1.38-19.09)*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3.59 (2.19-5.86)***</td>
</tr>
<tr>
<td>Male</td>
<td>2.31 (1.79-2.99)***</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, urbanization level
PY: person-years at risk
\( ^\d per1,000 \) person-years
\( ^* p<0.05, ^{**} p<0.01, ^{***} P<0.0001 \)
Analysis 2: ADHD and subsequent risk of epilepsy

- Prevalence for ADHD: 0.5%
- The mean age was 9 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.
Analysis 2: ADHD and subsequent risk of epilepsy

- 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 4. Hazard ratios for incidence of epilepsy with ADHD

<table>
<thead>
<tr>
<th>Hazard ratio and 95% CI</th>
<th>Unadjusted</th>
<th>adjusted#</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Patients with ADHD vs. comparison group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>4.14 (2.72-6.31)***</td>
<td>3.94 (2.58-6.03)***</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6</td>
<td>4.09 (2.05-8.19)***</td>
<td>3.79 (1.88-7.62)**</td>
</tr>
<tr>
<td>6-12</td>
<td>4.20 (2.28-7.76)***</td>
<td>4.16 (2.24-7.74)***</td>
</tr>
<tr>
<td>12-18</td>
<td>4.07 (1.43-11.62)**</td>
<td>3.84 (1.32-11.14)*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4.47 (1.90-10.54)**</td>
<td>4.44 (1.86-10.61)**</td>
</tr>
<tr>
<td>Male</td>
<td>4.04 (2.49-6.54)***</td>
<td>3.81 (2.34-6.21)***</td>
</tr>
</tbody>
</table>

# Adjusted for age, sex, urbanization level
PY: person-years at risk
\(^{†}\) per1,000 person-years
\(\ast p<0.05, \ast\ast p<0.01, \ast\ast\ast p<0.0001\)
Analysis 1: epilepsy and subsequent risk of ADHD

Previous retrospective studies:
- Children with epilepsy have a significant risk for ADHD, a prevalence of 12–39%,
- general pediatric population: 3-7%

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

Children with epilepsy had higher risk of developing ADHD
- adjusted HR=2.54, 95% CI=2.02-3.18
Discussion

Analysis 2: ADHD and subsequent risk of epilepsy

- Our sample (general population)
  - male : female = 4:1 (5:1)
  - Prevalence of ADHD = 0.5% (3-7%)

- population-based case-control study (n=109):
  - A history of ADHD was 2.5-fold more common among children with newly diagnosed seizures
  - The association was restricted to ADHD predominantly inattentive type (odds ratio [OR], 3.7; 95% CI, 1.1-12.8),
  - not ADHD predominantly hyperactive-impulsive type (OR, 1.8; 95% CI, 0.6-5.7) or
  - ADHD combined type (OR, 2.5; 95% CI, 0.3-18.3).

*Pediatrics 2001*
Analysis 2: ADHD and subsequent risk of epilepsy

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

- Children with ADHD had higher risk of developing epilepsy
  - adjusted HR=3.94,

Discussion

- Epileptic seizures can, by themselves, cause or aggravate ADHD
  - Epilepsy-induced impairment of networks

- ADHD and epilepsy
  - a common underlying causative factors,
    - including genetics and environmental factors
  - leading to a cascade of transcriptional changes in the brain (plasticity, apoptosis, neurogenesis)
  - alters behavior or cognition prior to the appearance of seizures.
Discussion

- **Limitation of our study:**
  - Which type of ADHD had higher risk of developing epilepsy is unknown
  - Diagnoses of ADHD using standard diagnostic criteria? underdiagnosis?
  - Factors other than mental retardation, e.g cerebral palsy, predicting attention problems were not excluded
  - Influence of AEDs/ADHD medication on subsequent seizure or inattention were not excluded

Discussion

- Are the child’s seizures adequately controlled?
- EEG monitoring: determine the presence of unrecognized seizure (particularly inattention, the predominant symptom)
- Subclinical EEG subtle effect: still controversial
- AED side effect: particularly on phenobarbital, benzodiazepines, gabapentin or topiramate
- Treatment with stimulant medication in most children with ADHD
Conclusion

- Early identification of ADHD and epilepsy comorbidity is crucial.

- Pediatrics neurologist should look for temporal relationships between the course of the epilepsy, and the onset of ADHD.

- In children with epilepsy, might need drugs combination to improve long-term cognitive and behavioral prognosis.

Children’s Medical Center, China Medical University & Hospital

Thanks for Your Attention!!