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

First Author, Year of Publication	Study Population	% With Hyperactivity or Combined	% With In attention
Onsted, 1955 [3]	830 children with epilepsy	8.4%	
Rutter, 1970 [4]	64 children with epilepsy	1.6%	
Holdsworth, 1974 [5]	85 children epilepsy	21%	42%
Bravidor, 1990 [6]	43 children <6 yr 60% intractable epilepsy	47%	
Hoare, 1991 [7]	108 children with poorly controlled epilepsy, 5-15 yr	48% (54% parent rating scales)	
Dunn, 2003 [8]	175 children with epilepsy for > 6 mo, 9-14 yr	14%	24%

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PLOS ONE

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

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March 2013 | Volume 8 | Issue 3 | e57926

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

Epilepsy ….. ↑ADHD

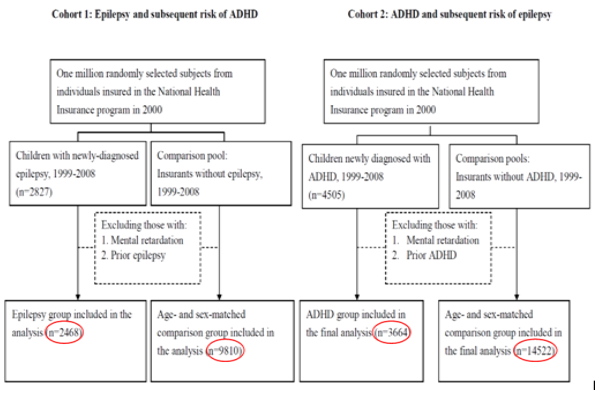
ADHD…..↑ Epilepsy

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

Cohort 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 2. Hazard ratios for incidence of ADHD with epilepsy

	Hazard ratio and 95% CI (Patients with epilepsy vs. comparison group)	
	Unadjusted	adjusted#
All	2.52 (2.01-3.17)***	2.54 (2.02-3.18)***
Age, years		
0-6	2.26 (1.74-2.93)***	2.26 (1.74-2.94)***
6-12	3.50 (2.13-5.74)***	3.53 (2.15-5.80)***
12-18	5.13 (1.38-19.09)*	5.30 (1.42-19.78)*
Sex		
Female	3.59 (2.19-5.86)***	3.59 (2.20-5.86)***
Male	2.31 (1.79-2.99)***	2.31 (1.78-2.98)***

#Adjusted for age, sex, urbanization level

PY: person-years at risk

†per1,000 person-years

*p<0.05, **p<0.01, ***P<0.0001

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).

Cohort 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

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

[#]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

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

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*

Discussion

- ADHD and epilepsy
  - 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

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 neurologist 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