An Overview of Attention Deficit Hyperactivity Disorder

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Overview

• Clinical Features
• Impact
• Genes, Environment and ADHD
Clinical Features of ADHD

- Bradley: benzedrine helps hyperactive children
- FDA approves methylphenidate for depression and narcolepsy
- Methylphenidate indicated for behavioral disorders in children
- US Surgeon General: lack of resources a "public crisis in mental health"
- CDC: ADHD a serious public health problem
- DSM IV revises criteria to include 3 subtypes of ADHD
- DSM III-R re-emphasizes hyperactivity
- DSM III ADD emphasizes attention
- ADHD symptoms described in medical literature as MBD
- Dr. George Still describes DMC syndrome in Lancet
- ADHD symptoms described in medical literature as MBD
- FDA approves methylphenidate for depression and narcolepsy
DSM-IV Criteria: Inattention

6 or more of the following—manifested *often*

- Inattention to details/makes careless mistakes
- Difficulty sustaining attention
- Seems not to listen
- Fails to finish tasks
- Difficulty organizing
- Avoids tasks requiring sustained attention
- Loses things
- Easily distracted
- Forgetful


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DSM-IV Criteria: Impulsivity/Hyperactivity

6 or more of the following—manifested *often*

**Impulsivity**

- Blurs out answer before question is finished
- Difficulty awaiting turn
- Interrupts or intrudes on others

**Hyperactivity**

- Fidgets
- Unable to stay seated
- Inappropriate running/climbing (restlessness)
- Difficulty in engaging in leisure activities quietly
- “On the go”
- Talks excessively

Variation in ADHD Symptoms

- Pervasiveness
- Frequency of occurrence
- Degree of impairment

ADHD Symptoms Change in Adolescence and Adulthood

- Hyperactivity
- Impulsivity
- Inattention

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- Time
The Persistence of ADHD into Adulthood

% With Persistent ADHD at Follow Up

Mean Age at Follow Up


Summary: Prevalence of Adult ADHD

Faraone & Biederman (Narrow)
Faraone & Biederman (Broad)
Kessler et al.
Family Studies
Community Studies
Longitudinal Studies (Full)
Longitudinal Studies (Residual)
Adult ADHD: Common but Not Commonly Treated

- Kessler et al. (2004)
- Biederman et al. (2004)
- Faraone et al. (2005)

<table>
<thead>
<tr>
<th>Percent Currently Treated</th>
</tr>
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<tr>
<td>0 2 4 6 8 1 0 1 2 1 4 1 6 1 8</td>
</tr>
</tbody>
</table>

Treatment with Stimulants in the Community

- No ADHD: 1%
- ADHD: 5.3%

Szatmari, et al., JAACAP, 2000
Treatment with Stimulants: A Rural Community Study

- No ADHD: 5%
- ADHD NOS: 22%
- ADHD: 72%

ADHD: Pediatric Comorbid Conditions

- Oppositional Defiant Disorder: 40%
- Language Disorder: 30–35%
- Anxiety Disorders: 20–25%
- Learning Difficulties: 15–25%
- Mood Disorders: 15–20%
- Conduct Disorder: 20%
- Smoking: 19%
- Substance Use Disorder: 15%

References:
1. MTA Cooperative Group. Arch Gen Psychiatry. 1999 Dec;56(12):1073-86.
Comorbidity in ADHD Youth from Primary Care and Psychiatric Settings


Developmental Progression of Comorbid Disorders

Cognitive Comorbidity: Functions Impaired in ADHD

• Executive dysfunction
  – Filtering interfering stimuli
  – Maintaining focus and shifting attention when necessary
  – Sustaining attention
  – Inhibiting inappropriate responses
  – Organizing complex information

Cognitive Comorbidity: Functions Impaired in ADHD (cont’d)

• Executive dysfunction (cont’d)
  – Planning
  – Holding information in working memory

• Specific learning disorders
  – Reading, writing, math
  – Sequencing
  – Abstraction

Neuropsychological comorbidity is associated with learning disabilities, school failure, and poor socialization
Impact of ADHD

Domains of Impairment

- Interpersonal relationships
  - Peer
  - Family
  - Authority
- School or occupational functioning
- Leisure activities
- Self-esteem
Impact on the Family

Parents of children with ADHD experience higher:

- Stress
- Self-blame
- Social isolation
- Depression
- Marital discord


Types of Change in Work Due to Child’s ADHD

- Stopped work 10%
- Altered work schedule 21%
- Reduced work hours 44%
- Changed type of job 14%
- Other 11%

Noe L. J Managed Care Pharm. 2001;7:133. Abstract.
Arrests and Speeding Violations
(Biederman, Faraone et al., J Clin Psychiatry, 2006)

Percentage Who Have Engaged in Each Behavior

- Been arrested
  - ADHD (N=500): 18%
  - No ADHD (N=501): 17%
  - P ≤ 0.01

- More than 1 speeding ticket in a 12-month period
  - ADHD (N=500): 25%
  - No ADHD (N=501): 25%
  - P ≤ 0.01

Relationship Problems as Adults
(Biederman, Faraone et al., J Clin Psychiatry, 2006)

Percentage of Each Group

- Ever divorced
  - ADHD (N=500): 28%
  - No ADHD (N=501): 15%
  - ** P ≤ 0.01

- Ever separated
  - ADHD (N=500): 10%
  - No ADHD (N=501): 5%
  - * P ≤ 0.01

Percent "Strongly Agree"

- Good relationship with parents
  - ADHD (N=500): 47%
  - No ADHD (N=501): 70%
  - ** P ≤ 0.001

- Fits in well with peers
  - ADHD (N=500): 40%
  - No ADHD (N=501): 70%
  - ** P ≤ 0.001

* P ≤ 0.01, ** P ≤ 0.001
Percent with Full-Time Employment by Academic Attainment
(Biederman, Faraone et al., J Clin Psychiatry, 2006)

Educational attainment is a factor in the difference in employment rates between those with ADHD and those without.
Statistically significant (P<0.001) difference within educational categories.

Mean Yearly Household Income
(Biederman, Faraone et al., J Clin Psychiatry, 2006)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ADHD (N=500)</th>
<th>Control (N=501)</th>
<th>P-value</th>
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<tr>
<td>Overall ($)</td>
<td>41,511</td>
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<td>Sex ($)</td>
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<tr>
<td>Female</td>
<td>45,645</td>
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<td>Male</td>
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<td>Age ($)</td>
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<td>18-24</td>
<td>41,742</td>
<td>39,494</td>
<td>NS</td>
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<tr>
<td>25-34</td>
<td>33,518</td>
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<td>35-49</td>
<td>44,981</td>
<td>67,196</td>
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<td>50-64</td>
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<td>63,212</td>
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<td>Race ($)</td>
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<tr>
<td>White / Caucasian</td>
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<td>Non-White</td>
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<td>46,030</td>
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<td>Marital Status ($)</td>
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<td>Married</td>
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<td>Not Married</td>
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<td>44,555</td>
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<td>Location ($)</td>
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<td>Urban</td>
<td>35,621</td>
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<tr>
<td>Rural</td>
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<td>50,587</td>
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<tr>
<td>Suburban</td>
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<td>61,427</td>
<td>&lt;0.1</td>
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ADHD and Medical Care Use for Children and Adolescents in Minnesota, USA


9-year Median Medical Costs for Children and Adolescents with and without ADHD

Genes, Environment and ADHD

ADHD Has a Substantial Genetic Component
(Faraone et al., Biological Psychiatry, 2005)

Mean Heritability of ADHD=.76
ADHD is an Environmentally Complex Disorder (Banerjee, Middleton & Faraone, Acta Pediatractica, in press)

- Pregnancy and Delivery Complications
- Exposure to Toxins
  - mercury, manganese, lead
  - polychlorinated bi-phenyls
- Fetal exposure to alcohol
- Fetal exposure to maternal smoking
- Chaotic family environments
- Low social class
Maternal Smoking & ADHD Risk Genes
(Neuman et al., Biological Psychiat, 2006)

Animal Models of Genetic and Environmental Effects in ADHD

• Compare gene expression in 6 brain regions of rats
  – Genetic model of ADHD (SHR)
  – Environmental model of ADHD (perinatal PCB)
    Q. Are the changes of ADHD candidate genes the same or different in the two models?

• Compare gene expression in brains of mice/rats in 2 experimental paradigms
  – In utero nicotine exposed (ongoing)
  – Developmental cigarette smoke exposed (with J. Zelikoff)
    Q. Are the changes of ADHD candidate genes the same or different as those in rat models?
Genes are clustered to reveal similar patterns in data. Genes that appear mostly all green or red are consistently changed by PCB exposure in SD rats compared to SHR rats vs three different background strains (Wistar, WKY, or Sprague-Dawley) - SD PCBvSD SHRvWKY SHRvSD.

Validation of changes in expression using qRT-PCR on individual RNA samples for 3 increased genes. NB: Overall confirmation of 29/30 observations (should all have positive slope). Also note that PCB effects confirmed as MORE robust than genetic model. Other genes validated: Synaptophysin, Period 2, Synaptotagmin.
**in utero** cigarette exposure effects on **IMAGE genes**

- Exposure to pregnant mouse dams equivalent to 1 pack/day, beginning at gestational day (GD) 4 thru GD 19
- No exposure after birth
- Examined IMAGE expression in 2 brain areas (SN-VTA, Vermis) in 8 young adult mice (4 male, 4 female)
- Focused on IMAGE genes with 2-fold changes

### IMAGE gene probes with 2 fold changes

<table>
<thead>
<tr>
<th>Probe Set ID</th>
<th>Gene Title</th>
<th>Symbol</th>
<th>Log2 Diff SN-VTA Female</th>
<th>Log2 Diff Vermis Female</th>
<th>Mean Diff</th>
<th>Note: MANY IMAGE genes are affected</th>
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<td>3.38</td>
<td>3.38</td>
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<td>2.03</td>
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<td>1.96</td>
<td>1.96</td>
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<td>-1.50</td>
<td>-1.50</td>
<td>-0.66</td>
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</tbody>
</table>
Environmental Regulation of Gene Expression

Gene expression depends on:
- can RNA polymerase II access the promoter?
- is the DNA bound to histone proteins acetylated or de-acetylated?
- are the CpG islands near the gene methylated or unmethylated?

Epigenetic gene probes with 2 fold changes

<table>
<thead>
<tr>
<th>Gene Title</th>
<th>Log2 DIF EN-VTA Males</th>
<th>Log2 DIF EN-TTA Males</th>
<th>Log2 DIF WT males</th>
<th>Log2 DIF WT females</th>
<th>Mean DIF</th>
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<td>Smad1-associated polypeptide 18</td>
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<td>2.10</td>
<td>1.92</td>
<td>1.38</td>
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<td>2.00</td>
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<td>1.23</td>
<td>0.82</td>
<td>0.65</td>
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<td>p53N (proliferation control of semen and synthesis of the 2 yolk)</td>
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<td>0.85</td>
<td>0.53</td>
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<td>methyl-CpG binding protein 2</td>
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<td>0.01</td>
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<td>DNA methyltransferase 36</td>
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<td>histone deacetylase 3</td>
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Summary

• Clinical Features
  – Hyperactivity, Impulsivity Intention
  – Psychiatric Comorbidity
  – Neuropsychological Dysfunction
  – Course into Adulthood

• Adverse impacts of ADHD seen in
  – School
  – Socialization
  – Driving
  – The workplace

Developmental Progression of ADHD

- Early Environmental Insults
  Maternal Smoking, Obstetric Complications

- Later Environmental Insults
  Substance use, social adversity

- Secondary Effects
  Low self esteem, school failure, social disability