Differential Diagnosis of ADHD
A Child Neurologist’s Perspective

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9th Annual UCSF Developmental Disabilities Conference
UCSF Child Neurology
March 12, 2010

What is ADHD?

* Attention-Deficit/Hyperactivity Disorder
  * most common neurobehavioral disorder of childhood
  * occurs in approximately 6–9% of school-aged children [Reiff 2003]

* behavioral diagnosis
  * inattention, impulsivity, & hyperactivity behaviors
  * no biological or psychological test(s) to “validate”

DSM-IV: Attention-Deficit/Hyperactivity Disorder

A.1.: ≥6 inattention symptoms for ≥6 months; maladaptive & inconsistent with developmental level

(a) poor attention to details or careless mistakes
(b) difficulty sustaining attention in tasks & activities
(c) not seeming to listen
(d) not following through on instructions & duties
(e) difficulty organizing tasks & activities
(f) avoids tasks with sustained mental effort
(g) loses things necessary for tasks or activities
(h) distracted by extraneous stimuli
(i) forgetful in daily activities

[DSM-IV-TR 2000]
**DSM-IV: Attention-Deficit/Hyperactivity Disorder**

A.2.: ≥6 hyperactivity/impulsivity symptoms for ≥6 months; maladaptive & inconsistent with developmental level

(a) fidgets or squirms  
(b) leaves seat  
(c) runs or climbs excessively  
(d) difficulty playing quietly  
(e) “on the go” or acts as if “driven by a motor”  
(f) talks excessively

(g) blurts out answers before questions completed  
(h) difficulty awaiting turn  
(i) interrupts others

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**DSM-IV: Attention-Deficit/Hyperactivity Disorder**

B. Impairment before age 7.

C. Impairment in ≥2 settings.

D. Clinically significant impairment in social, academic, or occupational functioning.

E. Not exclusively in PDD, schizophrenia, or other psychotic disorder; not better accounted for by another mental disorder.

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**DSM-IV: Attention-Deficit/Hyperactivity Disorder**

Types

<table>
<thead>
<tr>
<th>over past 6 months</th>
<th>A.1.</th>
<th>A.2.</th>
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</thead>
<tbody>
<tr>
<td>ADHD, Combined Type</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>ADHD, Predominantly Inattentive Type</td>
<td>✓</td>
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<tr>
<td>ADHD, Predominantly Hyperactive-Impulsive Type</td>
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Executive Dysfunction

- difficulties with:
  - organizing
  - planning
  - attending
  - decision making
  - self monitoring

- no definitive test of executive functioning

DDx of ADHD

- “ADHD” typically refers to idiopathic form
- Behaviors overlap with other conditions that look like ADHD or coexist with ADHD (mimics & comorbidities)
- May exist in the setting of another “more primary” neurologic or genetic disorder

Mimics: DDx of Behaviors

- inattention
- impulsivity
- hyperactivity / hyperkinetic movements
- poor organizational skills & other executive functions
Mimics: DDx of Behaviors

- normal variation
- dyslexia / learning disabilities
- language disorder
- “auditory processing disorder”? (auditory processing disorder)
- autistic spectrum disorders
- anxiety or other mental health disorders
- mental retardation
- academic talent/giftedness
- Tourette syndrome & other movement disorders
- hearing or visual impairment
- medication side effects
- substance use/abuse
- sleep disorder
- seizure disorder
- thyroid disorders
- anemia
- lead poisoning

DDx of Etiology

- Fetal Alcohol Spectrum Disorders
- Fragile X Syndrome
- Velocardioidal Facial Syndrome
- Neurofibromatosis, Type 1
- Tuberous Sclerosis
- Williams Syndrome
- Klinefelter Syndrome (47 XXY)
- Turner Syndrome (45 XO)
- 47 XYY
- Lead poisoning
- Static EncephaLopathy
- Neurodegenerative Disorders
- Myotonic Dystrophy

Differentiating amongst the Differential Diagnosis
Medical Evaluation: History

- **HPI**
  - developmental history
  - coexisting conditions
  - past medical history
  - family history
  - medications
  - substance use

- onset & course of ADHD symptoms
- psychological, medical, & developmental events as alternative explanation for symptoms

Medical Evaluation: History

- **HPI**
  - developmental history
  - coexisting conditions
  - past medical history
  - family history
  - medications
  - substance use

- unusual developmental patterns
- social relatedness
- verbal & non-verbal communication
- aspects of play & interests
- pre-reading & reading skills
- gross & fine motor skills
- clues to learning disabilities or autistic spectrum disorders

Medical Evaluation: History

- **HPI**
  - developmental history
  - coexisting conditions
  - past medical history
  - family history
  - medications
  - substance use

- most frequent: mental health disorders & learning disabilities
- Oppositional & Defiant Behaviors
- Depression
- Anxiety
- Misconduct
- Obsessive-Compulsive Disorder

- 1 or more in up to 1/2 of school-aged children with ADHD [Reiff 2003; Krull 2009]
- screening questions [Reiff 2003]
Medical Evaluation: History

- HPI
- developmental history
- coexisting conditions
- past medical history
- family history
- medications
- substance use

- pre-natal & perinatal history
- failure to thrive
- recurrent or chronic otitis media
- visceral anomalies
- h/o head injury
- h/o meningitis/encephalitis
- seizures

Medical Evaluation: History

- HPI
- developmental history
- coexisting conditions
- past medical history
- family history
  - medications
  - substance use
- ADHD behaviors, learning disabilities, psychiatric disorders, or behavior problems
- mental retardation
- Fragile X syndrome
- neurodegenerative disorders

Medical Evaluation: History

- HPI
- developmental history
- coexisting conditions
- past medical history
- family history
  - medications
  - substance use
- anticonvulsants (some)
- antihistamines
- antipsychotics
- corticosteroids
- beta-blockers
- bronchodilators
Medical Evaluation: History

- HPI
- developmental history
- coexisting conditions
- past medical history
- family history
- medications
- substance use
- illicit substances
- alcohol
- caffeine

Medical Evaluation: Exam

- vision & hearing checks
- abnormal head size
- facial or somatic dysmorphic features
- skin examination
- organ anomalies
- neurologic examination
  - r/o focal signs
  - ± neurodevelopmental tests

Medical Evaluation: Testing

- not justified in routine ADHD evaluation:
  - labs
  - neuroimaging
  - EEG/qEEG
  - continuous performance tests
  - neuropsychological tests of executive function
- only as indicated by other clinical factors

[Reiff 2003]
Specific Neurological Disorders

Autistic Spectrum Disorders & ADHD
- Symptoms meeting criteria for ADHD in up to 78% of those with autistic spectrum disorders [Goldstein 2004; Lee 2006; McCarthy 2007]
- Stimulants first-line treatment for ADHD symptoms in ASD [Aman 2007]
  - Work less well than in idiopathic ADHD (on average)
  - Elevated risk of adverse events
  - “Start low, go slow”

Mental Retardation & ADHD
- ADHD symptoms more common in children with MR (9–16%) [Handen 2006]
- True prevalence of ADHD in MR unclear [Hastings 2005; Antshel 2006; Deutsch 2008]
  - Diagnostic controversies
  - Stimulants first line for ADHD in MR [Handen 2006]
  - May be at greater risk for experiencing side effects [Handen 2006] – “Start low, go slow”
**Tourette Syndrome & ADHD**

- 50–80% of individuals with Tourette syndrome have comorbid ADHD [Dunn 2003; Cavanna 2009]
- ask about tics in any patient with ADHD
- assess for and treat most problematic symptoms [Cavanna 2009]
- randomized placebo-controlled trial and meta-analysis of various other studies found no exacerbation of tics with stimulants [Erenberg 2005; Kenney 2009; Jimenez-Shahed 2009]

**Daydreaming or seizing?**

- daydreaming / inattentiveness
  - during classroom & homework time (situation-dependent)
  - prolonged
  - awareness of daydreaming

**Seizures**

- absence seizures
  - brief (<30s), repetitive, frequent spells of staring
  - situation-independent & can interrupt activity
  - abrupt start & end
  - unaware of events during episode
  - slight motor behaviors (e.g. eyelid flutters) or possible automatisms

- complex partial seizures
  - infrequent; usually >30s
  - automatisms & lateralizing motor features
  - possible aura & post-ictal confusion
**Epilepsy & ADHD**

- 14–40% of children with epilepsy exhibit ADHD [Kaufmann 2009; Dunn 2004; Aldenkamp 2006]
- Inattentive type most prevalent [Kaufmann 2009; Kanner 2008]
- Antiepileptic Medications [Dunn 2004; Coppola 2004; Chung 2008]
  - **barbiturates** (phenobarbital) & benzodiazepines – inattention & hyperactivity
  - findings equivocal on many other AED medications
  - **levetiracetam** – psychiatric & behavioral symptoms (e.g. aggression, hyperactivity, & agitation) in non-controlled pediatric studies

**Epilepsy & ADHD**

- Stimulants
  - Physicians’ Desk Reference lists seizure as possible effect; recommends discontinuation if seizures occur [Kanner 2008]
  - BUT... [Schubert 2005; Raspall-Chaure 2008; Kaufmann 2009]
  - no clear evidence that methylphenidate or dextroamphetamine aggravates or induces epilepsy
  - no contraindications to stimulants in epilepsy
  - EEG only if clinical suspicion
  - Avoid bupropion

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**Fetal Alcohol Spectrum Disorders**

- Fetal Alcohol Syndrome (FAS), Partial FAS, & Alcohol-Related Neurodevelopmental Disorder (criteria-based):
  - prenatal EtOH exposure
  - poor growth
  - abnormal brain growth/structure
  - facial features (short palpebral fissures, smooth philtrum, thin upper lip, flat midface)
  - behavioral or cognitive abnormalities

[Photos from Wattendorf 2005b]

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**FAS Disorders: Behavioral or Cognitive Abnormalities**

- ADHD in up to 70% [Pearl 2001; Kooistra 2009a; Nash 2006]
  - possibly less responsive to stimulants (limited data) [Kooistra 2009b]
- speech & language delays, verbal & nonverbal learning problems, and executive function deficits

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**Fragile X Syndrome**

- Most common inherited cause of mental retardation
- ADHD in nearly all males & 50% of females [Phalen 2005]
- Other behavioral features: social avoidance, poor eye contact, aggression, anxiety, & unusual responses to sensory stimuli
- Physical features: long face; large ears; low muscle tone & hyperextensible joints; large testicles
  - boys: behavioral & physical differences; girls: more subtle (sometimes ADHD & learning disabilities)
- DNA testing if FHx of MR, esp. males
- 10/15 “clinical responders” to methylphenidate in one double-blind study [Reiss 2007]

[Photos from Wattendorf 2005a; Penagarikano 2007]
Velocardiofacial Syndrome
(22q11.2 deletion syndrome)

- ADHD is most common psychiatric problem associated with VCFS (35–55%)
- most often inattentive subtype
- also anxiety & social withdrawal
- as adults, high schizophrenia risk
- low borderline general cognitive ability
- significant visuospatial dysfunction, diminished math attainment, & executive dysfunction

[Gothelf 2003, 2004; Antshel 2005, 2008]

VCFS Physical Features

- Congenital cardiac anomalies (tetralogy of Fallot, VSD with pulmonary atresia, persistent truncus arteriosus, & interrupted aortic arch)
- Dysmorphic facies: hypoplastic alae nasi, prominent nasal root, long face with flat cheeks, narrow eye opening, small mouth & retruded chin, and small-cupped ears Palatal abnormalities with hypernasal speech
- Hypocalcemia (hypoplastic parathyroid)
- T-cell immunodeficiency (hypoplastic thymus)
- Others: tortuous retinal vessels, growth retardation, juvenile rheumatoid arthritis, & urinary anomalies

[Gothelf 2007]

VCFS & ADHD Management

- cytogenetic testing recommended only for ≥2 major signs/symptoms [Gothelf 2007]
- single open-label study of stimulant use in VCFS [Gothelf 2003]
  - methylphenidate for 1 month effectively & safely reduced ADHD symptoms in 75%
  - no psychotic or manic symptoms
Neurocutaneous Disorders:
Neurofibromatosis type 1 (NF1)

- 30-50% with NF1 have ADHD [Levine 2006; Acosta 2006]
- learning disabilities also prominent (35–65%) [Levine 2006]
- physical manifestations:
  - café-au-lait spots; axillary/inguinal freckling; iris hamartomas (Lisch nodules)
  - osseous lesions (sphenoid wing dysplasia, pseudoarthrosis)
  - benign & malignant neural tumors (neurofibromas, optic gliomas)
- improvements in cognitive, academic, & social problems of children with NF1 & ADHD with stimulants [Mautner 2002]

Neurocutaneous Disorders:
Tuberous sclerosis complex (TSC)

- dominantly inherited disorder of cell differentiation & proliferation
- affects brain, skin, kidneys, heart, lungs, & other organs
- mental retardation, epilepsy, &/or autism in 85% [Curatalo 2008]
- ADHD reported in 30–60% [D’Agati 2009]
- ADHD more frequent in individuals with TSC with ASDs [D’Agati 2009]

Neurocutaneous Disorders

- ADHD also seen in Sturge-Weber syndrome & other neurocutaneous disorders
- underscore importance of skin examination
- all warrant evaluation by neurologist
Static Encephalopathy

- perinatal asphyxia / neonatal encephalopathy
- survivors without major neurological abnormalities more likely to have ADHD [Gonzalez 2002]
- prematurity
  - predisposes to ADHD [Pearl 2001; van Baar 2009; Aarnoudse-Moens 2009]
- traumatic brain injury [Dunn 2003; Max 2005a, 2005b]
- associated with impaired attention, impulsivity, and hyperactive ("secondary ADHD")
- severity of injury & location (frontal lobes & subcortical gray matter) have been found as predictive factors

X-linked Adrenoleukodystrophy

- neurodegenerative white matter disease
- 4-8 y.o. boys with behavioral/academic concerns (often ADHD)
- overt neurologic dysfunction later; progressive decline & death
- plasma VLCFA; newborn screen likely available soon
- therapies (adrenal replacement, Lorenzo's oil, hematopoietic stem cell transplant) may improve prognosis of X-ALD when offered early, but no definitive cure
  [Pearl 2001; Moser 2005; Listernick 2009]

X-linked Adrenoleukodystrophy

- Watch out for:
  - FHx: multiple sclerosis, adrenal insufficiency, early deaths
  - motor impairments (spasticity, hyperreflexia, dysrhythmic speech, ataxia)
  - declines in cognition, learning, behavior, or emotional regulation
  - late-onset attention/learning problems; visual-spatial difficulties
  - others (e.g. metachromatic leukodystrophy) can present with ADHD
Conclusions

- ADHD remains a behaviorally-defined disorder
- many learning & mental health disorders that can mimic ADHD are also common comorbidities
- treatable medical disorders can mimic ADHD symptoms
- other neurogenetic & neurologic disorders can underlie the ADHD behavioral diagnosis
- all must be considered when evaluating a child with ADHD; further evaluation as clinically appropriate
- except for treatable medical mimics, stimulants remain first-line medication when ADHD occurs in the setting of another neurologic/neurogenetic condition

Differential Diagnosis of ADHD

A Child Neurologist's Perspective

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References (suggested readings with * and in bold)


Goldstein, S., & Schwebach, A. J. (2004). The comorbidity of pervasive


