The Development and Boundaries of the ADHD Construct: Historically Unique Features and Differential Diagnosis

Andrew Potash, LPC
Sansea Jacobson, MD
3rd Annual Conference on ADHD and Executive Function
Sheraton Station Square, Pittsburgh, PA
September 5th, 2014

Objectives

- Historical Perspectives
- Defining Attention Deficit Hyperactivity Disorder (ADHD)
- Risk and Prognostic Factors
- Case vignette
- Differential Diagnosis
- Wrap-up

“Fidgety Phil”


(Thome & Jacobs, 2004)
The Three Pillars of ADHD

• Inattention
• Hyperactivity
• Impulsivity

Early History

• Sir Alexander Crichton (1798)
  – Observed children “incapable of attending with constancy”
• Sir George Frederic Still (1902)
  – Described symptoms as a “defect of moral control” with “biological determinants”
• Kramer and Pollnow (1932)
  – Named “hyperkinetic disease of childhood”

(Barry, 2009; Baumeister et al., 2010; Crichton, 1798/1976; Lange et al., 2010)

Early History

• Post-encephaletic behavior disorder (1917-1926); Electroencephalography (EEG)
• Charles Bradley (1937)
  – Noticed that Benzedrene stimulant had behavioral inhibition as side effect
• Leandro Panizzon (1944)
  – Synthesized methylphenidate

(Baumeister et al., 2010; Bradley, 1937; Lange et al., 2010)
ADHD in the DSM

• DSM-II (1968): Hyperkinetic Reaction of Childhood
• DSM-III (1980): ADD (with or without hyperactivity)
• DSM-III-R (1987): ADHD
  – No subtypes, led to an increase in diagnoses
• DSM-IV (1994): ADHD again divided into subtypes, opened diagnosis to adults
• DSM-5 (2013):
  – Subtypes now included as specifiers
  – Maximum age of onset moved from 7 to 12
  – Classified as neurodevelopmental, rather than behavioral, disorder
• World Health Organization’s International Classification of Diseases ICD-10 (1992): Hyperkinetic Disorder

Development of ADHD within a cultural context

Conceptualization of ADHD:

  Moral → Medical → Behavioral → Neurodevelopmental

Rise in the 1960s

• Ritalin approved by FDA in 1961
• DSM-II diagnosis of Hyperkinetic Reaction in 1968
Decline in the 1970s and 1980s

- Negative publicity in early 1970s over “drugging of problematic children”
- Negative media; lawsuits against physicians, school, and APA in late 1980s

(Mayes et al., 2008)

Boom in 1990s

From 1991-2001, spending per child on stimulants grew almost ninefold, and prescriptions increased sixfold

Contributing factors:
- Medicaid public health insurance expansions
- SSI expanded to include low-income youth with ADHD
- IDEA expanded to include ADHD as a protected disability
- Managed care companies’ increasing demands on PCPs and making it more difficult to see specialists
- Ritalin’s patent expired in mid-80s allowing for cheaper, generic methylphenidate
- CHADD (lobbying and support group) founded in 1987
- DSM-IV opened diagnosis of ADHD to adults

(Mayes & Schulsinger, 1998)

Continued Upward Trend

- Based on the National Survey of Children’s Health, from 2003-2007 ADHD rates increased by an average of 5.6% each year.
- A parent-reported history of ADHD increased by 42% from 2003 to 2011.
- Now 7.2% of all school-aged children in the U.S. are currently assigned a diagnosis of ADHD, and 11% have carried a diagnosis at some point in their lives.
- More than two-thirds of those with current ADHD were taking medication for treatment in 2011.
- Prevalence of medicated ADHD increased by 28% from 2007 to 2011.

(Moore et al., 2016)
U.S. leads the world in ADHD rates and stimulant medication use

- The United States accounts for 80-85% of the world's psychostimulant use.

- By comparison, in France, 0.05% of children (1 in 2000) are prescribed stimulant medications for ADHD.
  - What factors might account for this gap? (Vallee, 2009)

Cultural/Environmental Factors

- Gender
  - ADHD presents 2:1 boys:girls and 1.6:1 in adults, but boys are identified 4:1 in healthcare settings

- Risk Factors
  - Diet
  - Sleep
  - Exercise/Activity
  - Information overload/Multitasking

(APA, 2013; Rowland et al., 2002)

Societal Changes

- Family Structure
- Classroom Size
- Prevalence of Multimedia
- Poverty Rates
- Nutritional Patterns
- Sleep Patterns
- Environmental Exposures

(Mayes & Eccleston, 2009; Stolzer, 2005; Thakkar, 2013)
Case Vignette

Risk and Prognostic Factors – Genetics (1)

- The heritability of ADHD is substantial
  - Mean heritability of ADHD is around 79% (Laikiv et al., 2010)

- Heritability of ADHD
  - Family studies
    - 2-8x risk in parents and siblings (Biederman, 2005)
  - Twin studies
    - Monozygotic > dizygotic concordance (Thapar, 1999)
  - Adoption studies
    - Increased risk in biologic parent vs. adoptive (Sprich, 2000)

Risk and Prognostic Factors – Genetics (2)

- *Some promising (DA/NE) Susceptibility Genes*
  - **DRD4** (7-repeat allele of VNTR in exon III), OR=1.27, x4 studies
  - **DRD5** (148-bp microsatellite repeat), OR=1.22, x4 studies
  - **DAT1** (440-bp VNTR in 3' UTR), OR=1.1, Replicated in 2 studies

- Rare genetic variants
  - Some rare chromosomal anomalies have been found to be associated with higher rates of ADHD
    - Fragile X
    - Tuberous sclerosis
    - Microdeletions (Smith Magenis, Velocardiofacial 22q11)
Temperament

- ADHD is associated with reduced behavioral inhibition, effortful control, or constraint; negative emotionality; and/or elevated novelty seeking.
- These traits may predispose some children to ADHD but are not specific to the disorder.

Gender

- ADHD is more frequent in males than in females in the general population, with a ratio of approximately:
  - 2:1 boys to girls (Polanczyk et al. 2007)
  - 1.6:1 men to women (Kessler et al. 2006)
- Females are more likely than males to present primarily with inattentive features.
- Boys are identified 4:1 in healthcare settings.

While specific genetic factors have been correlated with ADHD they are neither necessary nor sufficient causal factors.

Maternally related prenatal risks

- Prenatal exposure to D&A
  - Cigarette smoking with consistent, dose-response relationship (OR=2.39) (Langley, 2005)
  - Alcohol use during pregnancy can result in FAS with known inattention/hyperactivity (Koivukangas, 2000)
- Maternal health factors (e.g. obesity)
• Pregnancy and Birth Complications
  – Prematurity (RR=2.64) with risk strongest for extreme prematurity and low birth weight (Aarnoudse-Moens, 2009)
  – Very low birth weight
    • VLBW (less than 1,500 grams) conveys a 2- to 3-fold risk for ADHD, but most do not develop ADHD.
    • Although ADHD is correlated with smoking during pregnancy, some of this reflects common genetic risk (Thapar et al. 2009).
  – Other factors
    • Bleeding in pregnancy, protracted delivery, low APGAR, intrauterine growth restriction, etc.

• External agents (causality remains unclear)
  – Exposure to toxins have been correlated with ADHD
    • Lead
    • Organic Pollutants (polychlorinated biphenyl, pesticides, etc)
  – Diet and Nutritional factors
    • Artificial food colorings, Zn, Fe, Mg, sugar
  – Other
    • Infection, Sleep, Exercise, Activity, Information overload, multitasking, low parental education, low SES, bullying, maltreatment and family discord

All of the above environmental factors have shown higher association with ADHD although causality remains unclear

Risk and Prognostic Factors – Environment (2)

Risk and Prognostic Factors – Environment (3)

Poor School Performance

Are there deficits in Intellectual function and deficits in adaptive functioning?

Yes

No

Are there deficits in Social use of communication?

Yes

No

Are there deficits in developing and maintaining social relationships, deficits in social-emotional reciprocity; and restricted repetitive patterns?

Yes

No

Intellectual Development Disorder (IDD)

Autism Spectrum Disorder (ASD)

Social Communication Disorder

...
Are there persistent difficulties in the acquisition and use of language?

Yes (standardized language ability tests and clinical assessment)

Specific Learning Disorder

No

Language Disorder

No

Selective Mutism

Specific Learning Disorder

Are there difficulties in learning and using academic skills?

Yes (standardized achievement measures and clinical assessment)

Conduct Disorder

No

Executive-Ritual

Dysregulation Disorder (ERD)

No

Oppositional Defiant Disorder (ODD)

Are there severe temper outbursts accompanied by chronic anger/irritability?

Yes (Comprehensive Clinical Assessment)

Substance Use Disorder

No

Separation Anxiety

Are there severe temper outbursts accompanied by chronic anger/irritability?

Yes (Comprehensive Clinical Assessment)

Separation Anxiety

No

Adjustment Disorder

Are there difficulties in learning and using academic skills?

Yes

Poor School Performance DSM-5 Differential Diagnosis (2)

No

Are the problems related to a substance and do symptoms remit when substance removed?

Yes

Substance Use Disorder

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Separation Anxiety
Poor School Performance DSM-5 Differential Diagnosis (5)

Is the school performance difficulty associated with symptoms of inattention and/or hyperactivity-impulsivity with clear evidence of interference and with functioning?

Yes

No

Not related to a mental disorder e.g. excessive behavioral in active child, poor work habits, understimulating environment for gifted child, disruptive environment, hearing/medical issues, etc.?

Yes

No

A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   - careless mistakes
   - sustaining attention
   - does not seem to listen
   - does not follow through
   - difficulty organizing
   - avoids tasks that require sustained mental effort
   - loses things
   - easily distracted
   - forgetful

   **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   - fidgets
   - leaves
   - runs about or climbs
   - unable to play or engage in leisure activities
   - “driven by a motor”
   - talks excessively
   - blurts out
   - difficulty waiting turn
   - interrupts or intrudes

   **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
• ADHD is characterized by symptoms of inattention and/or hyperactivity-impulsivity – that are inconsistent with developmental level – that negatively impact social and academic/occupational activities – and must be differentiated from . . .

In contrast to Attention-Deficit/Hyperactivity Disorder . . .
Oppositional Defiant Disorder or Conduct Disorder

ODD / CD
Resistance to work due to refusal to submit to others' demands accompanied by negativity, hostility, and defiance

ADHD
Aversion to work due to difficulty in sustaining attention, forgetting instructions, procrastination, and impulsivity

Intercurrent Explosive Disorder (IED)

IED
Characterized by high levels of impulsive behavior, but unlike ADHD, there are episodes of serious impulsive aggression toward others.

ADHD
Chronic impulsivity in ADHD can contribute to misbehavior, irritability, and poor self-control without serious aggression

Disruptive Mood Dysregulation Disorder (DMDD)

DMDD
Frequent severe temper outbursts (3x/wk x12mo) with severe nonepisodic irritability

ADHD
Episodes of irritability are generally triggered by frustration related to inattention, impulsivity, hyperactivity

***DMDD is placed in the class of depression disorders because longitudinal follow-up evidence predicts emergence of depressive disorders both in a short-term follow-up of two years and long-term of 20 years later
Anxiety and Trauma-Related Disorders

Difficulties concentrating and physical restlessness are related to fear and worry, rumination, intrusive thoughts or images, and other trauma or anxiety symptoms.

ADHD

Inattention and hypomotoric behavior is due to attraction to external stimuli or new activities, or preoccupation with preferred, less cognitively taxing activities.

Bipolar (BD) and Depressive Disorders (DD)

BD

May show hyperactivity, impulsivity, irritability and distractibility, and these features are episodic and accompanied by other specific features of hypomania.

DD

May show inattention, irritability, difficulty completing tasks; however, these symptoms are episodic and accompanied by specific features of depression.

ADHD

May exhibit mood lability throughout the day. However, it is non-episodic and accompanying features of a major mood disorder are not present.

Comorbidity

1. The risk for comorbidity is high in ADHD
   - ODD in ~50% of children with ADHD-CT (~25% for ADHD-IT)
   - Depression occurs in approximately 20% to 30% of ADHD patients
   - Anxiety occurs in more than 25% of patients.
   - Learning disorders co-occur with ADHD 20-40%
   - SUDs are significantly more frequent among adults with ADHD
   - Many other diagnoses are known to co-occur, e.g. OCD, Tics, ASD, CD, etc.

2. It is critical to diagnose and treat these accompanying diagnoses, because patients with comorbidities experience greater cognitive, social, and psychological impairments!
Final Considerations for Case Vignette

- What diagnostic workup would you want next?
- With whom would you want to speak?
- What additional information would you want to collect?

Summary

- Historical perspectives of ADHD demonstrate cultural and societal changes which have contributed to increased awareness and intervention.
- Pathophysiology of ADHD remains uncertain:
  - Although ADHD is highly heritable, specific genetic factors are neither necessary nor sufficient causal factors.
  - Although certain environmental factors have higher correlation with ADHD, there is unclear causation.
- The core symptoms of ADHD show tremendous symptom overlap and comorbidity with other pathological and non-pathological states.
- When approaching the differential diagnosis of ADHD, one must cast a wide net.

Questions?