Attention Deficit Hyperactivity Disorder (ADHD)

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ADHD - most common emotional, cognitive, and behavioral disorder pediatricians, family physicians, neurologists, and psychiatrists treat in children!

Gr. *aprosexia* - "attentional disturbance" or "failure to heed".

CLINICAL FEATURES

Term "attention deficit" is misleading

- rather than too little attention, many patients pay too much attention to too many things, leading them to have little focus.
- patients have difficulty regulating attention; difficulty inhibiting attention to nonrelevant stimuli, and/or focusing too intensely on specific stimuli to exclusion of what is relevant.

6 major TASKS OF EXECUTIVE FUNCTION that are most commonly distorted:

1) flexibility (i.e. shifting from one mindset or strategy to another)
2) organization (e.g. anticipating both needs and problems)
3) planning (e.g. goal setting)
4) working memory (i.e. receiving, storing, then retrieving information within short-term memory)
5) separating affect from cognition (i.e. detaching one's emotions from one's reason)
6) inhibiting and regulating verbal and motoric action (e.g. jumping to conclusions too quickly, difficulty waiting in line in appropriate fashion).

Diagnosis is clinical (at present, no laboratory studies, imaging studies, or procedures help with diagnosis of ADHD)!

Short attention span, difficulty concentrating, impulsivity, distractibility, excitability, hyperactivity

All of following *DSM-IV* criteria for ADHD must be present:

1. Either criteria for **inattention** or criteria for **hyperactivity/impulsivity** must be met:

Inattention: at least 6 of 9 symptoms must have persisted for at least 6 months to degree that is *maladaptive* and *inconsistent with patient's developmental level*:

1) often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
2) often has difficulty sustaining attention in tasks or play activities.
3) often does not seem to listen when spoken to directly.
4) often does not follow through with instructions and does not finish schoolwork, chores, or duties in workplace (not because of oppositional behavior or failure to understand instructions).
5) often has difficulties with organizing tasks and activities.
6) often avoids, dislikes, or is reluctant to engage in homework that requires sustained mental effort.
7) often loses things necessary for tasks or activities (e.g. school assignments, pencils, books, tools, toys).
8) often is easily distracted by extraneous stimuli.
9) often is forgetful in daily activities.

Hyperactivity/impulsivity: at least 6 of 9 symptoms have persisted for at least 6 months to degree that is *maladaptive* and *inconsistent with patient's developmental level*:

1) often fidgets with hands or feet or squirms in seat.
2) often leaves seat in classroom or in other situations in which remaining seated is expected.
3) often runs around or climbs excessively in situations in which this behavior is inappropriate (adolescents or adults may be limited to subjective feelings of restlessness).
4) often has difficulty playing or engaging in leisure activities quietly.
5) often on go or often acts as if driven by motor.
6) often talks excessively.
7) often blurts out answers to questions before questions are completed.
8) often has difficulty waiting turns.
9) often interrupts or intrudes on others (e.g. butts into conversations or games).

2. Onset occurs no later than age of 7 years. *most commonly before age 4 yrs*

3. Symptoms must be present in ≥ 2 situations (e.g. school, work, home), i.e. symptoms are pervasive; however, may not all occur in all settings.

communication with teachers, special educators, psychologists, parents must occur to explore all settings

4. Disturbance causes clinically significant distress or impairment in social, academic, or occupational function.

5. Behavior does not occur exclusively during course of pervasive developmental disorder, premenstrual dysphoric disorder, schizophrenia, or other psychotic disorder. No mood, anxiety dissociative, or personality disorder accounts for behavior.

- child usually seems most awake in late evening (awakening child for school causes major problems).
- **hyperactivity** is defined subjectively - increase in motor activity to level that interferes with child's functioning.
- ADHD girls have lower rates of disruptive behavior (than boys).
- clumsiness and learning disability are secondary features! (but only ≈ 30% ADHD children are learning-disabled)
- significant ***psychiatric comorbidity*** - 50-60% patients meet DSM criteria for at least 1 coexisting condition (learning disorders, restless-legs syndrome, ophthalmic convergence insufficiency, depression, anxiety disorder, antisocial personality disorder, substance abuse disorder, conduct disorder).
- no *somatic comorbidities* are significantly associated with ADHD.

DSM-IV distinguishes three types:

1. ADHD, predominantly inattentive type (20-30%; boys ≈ girls)

2. ADHD, predominantly hyperactive-impulsive type (< 15%; boys >> girls)
3. ADHD, combined type (50-75%)

N.B. symptoms of attention deficit disorder may exist with or without hyperactivity!

Course

- 75% ADHD children continue to have disorder as adolescents, and 50% as adults.
- *hyperactive symptoms* may decrease with age (developmental self-control); *inattentive symptoms* do not appear to have similar developmental advantage and tend to remain constant into adulthood.

ASSESSMENT INSTRUMENTS

Neuropsychological testing is not required to diagnose ADHD!

IQ tests

- untimed tests are most appropriate.
- large discrepancy between patient's IQ and other measures, such as visual or auditory abilities or ability to work with numbers, is not uncommon.
- many people in whom ADHD is not diagnosed until later years have IQs well above average but function, such as short-term memory, that is at or below average.
- perform learning-disability (LD) evaluation (**IQ** versus **academic achievement**).

Gauging:

1. Conner's questionnaire (administered to parents or teachers).
2. Written / computerized tests of attention.
3. Accelerometer on wrist
4. Gauge under seat of child's chair

DIFFERENTIAL DIAGNOSIS

Conditions that may cause hyperactivity:

1. **Sedative-hypnotics** paradoxically cause hyperactivity in some children.
2. **Depression** - sad feelings may be expressed by increased activity.
3. **Anxiety**
4. **Severe CNS disease** (grossly abnormal CNS, significant head trauma).
5. **Constitutional hyperactivity** is present from birth.
6. **Factitious hyperactivity** - intolerant parent, teacher, or supervisor.
7. **Specific learning disabilities** may be associated with hyperactivity.
8. Severe **language disorders**
9. **Tourette disorder**

PATHOPHYSIOLOGY, NEUROIMAGING

Frontal cortex and circuits linking them to **basal ganglia** are critical for executive function and, therefore, to attention and exercise inhibition.

- executive functions are major tasks of frontal lobes.
- MRIs in patients show *decreased activation (low arousal) of right mesial prefrontal cortex* during tasks that require inhibition of planned motor response and timing of motor response to sensory cue.
- MRIs in patients show *weakened activity in right inferior prefrontal cortex* and *left caudate* during task that involves timing of motor response to sensory cue.
- catecholamines are main neurotransmitters with frontal-lobe function (***dopaminergic*** and ***noradrenergic*** neurotransmission are main targets for ADHD treatment).
- 10-year study by National Institute of Mental Health (NIMH) demonstrated that brains of children and adolescents with ADHD are 3-4% smaller (more severe ADHD symptoms, smaller frontal lobes, temporal gray matter, caudate nucleus, and cerebellum).

EEG

Neuropsychiatric EEG-Based Assessment Aid (NEBA) System - FDA-approved, brain function – based medical device for use in diagnosis of ADHD in children aged 6-17 years.

- NEBA system calculates ***ratio of theta and beta brain waves***, which is comparatively high in children and adolescents with ADHD.
- not meant to be used alone as a means of confirming presence of ADHD; but can be employed in combination with complete medical and psychological assessment to help confirm diagnosis / to indicate direction that further testing should take.
- NEBA device should not be used in individuals with a history of EEG abnormalities, seizure disorder, on anticonvulsants, or with a metal plate or device in the head

EPIDEMIOLOGY

PREVALENCE in children 3-9%, in adults ≈ 4.4%.

- positive family history rises risk significantly.
- **male**-to-female ratio = 2-4 : 1 (underidentification in girls remains major concern).

ETIOLOGY, GENETICS

ADHD is one of the most highly heritable of all psychiatric disorders (heritability 0.60-0.95)

- studies have revealed several genes associated with ADHD with effect on dopamine receptors, dopamine transport, and dopamine beta-hydroxylase.

TREATMENT

Healthy **diet** with minimal, if any, caffeine.

- no evidence that avoidance of sugar, foods with red dye or rich in salicylates, and megadoses of vitamins help.

Because regular **physical activity** is important in improving concentration, it may be important component of therapy.

BEHAVIORAL CARE

Despite symptomatic deficits, children must still be held accountable for their behavior and its consequences!

- **school / education interventions** (traditional classrooms and academic activities often exacerbate ADHD);
  - ADHD children concentrate better in front row than in rear.
  - study carrels [*angl*. darbo kabina] are helpful - block distracting stimuli.
  - low student-teacher ratios (i.e. one-on-one instruction or small groups).
  - frequent breaks with opportunity to move about.
  - teachers have important function - periodic feedback about child's school performance through use of standardized scales, narrative descriptions, and telephone follow-up.

- **psychotherapeutics**.

PHARMACOTHERAPY

Sedatives should be avoided because some (notably phenobarbital) may precipitate ADHD!

Neuroleptics are contraindicated!

PSYCHOSTIMULANTS

- first-line agents for ADHD - effective and lack major adverse effects when used at therapeutic doses.

- increase amount of intrasynaptic *dopamine* and *norepinephrine* → stimulate areas of decreased activation to higher state of arousal.
- all are schedule II controlled substances; rate of abuse* among patients is very low (but not zero!).
  *medication treatment of ADHD reduces risk of future substance abuse by almost 2-fold!

1. METHYLPHENIDATE (Ritalin, Methylin, Concerta) - one of safest pharmaceuticals used in children! (available for > 40 years). see p. A35 >>
2. DEXMETHYLPHENIDATE (Focalin, Focalin XR) - pharmacologically active d-enantiomer of racemic METHYLPHENIDATE. see p. A35 >>
3. DEXTROAMPHETAMINE (Dexedrine, Dextrostat) see p. A35 >>
4. MIXED AMPHETAMINE SALTS (Adderall) - DEXTROAMPHETAMINE and AMPHETAMINE mixture.
5. LISDEXAMFETAMINE DIMESYLATE (Vyvanse) - prodrug of DEXTROAMPHETAMINE.
6. Magnesium PEMOLINE (Cylert); no longer produced due to risk of liver toxicity!
7. GUANFACINE extended-release tablets (**nonstimulant** selective α2A-adrenergeic receptor agonist) - FDA approved adjunctive to stimulants.

- drugs are available as:
  1) **short-acting, immediate-release** (IR) preparation
  2) **extended-release** preparations (e.g. continuous release [CR], sustained release [SR], osmotic-release oral system [OROS]) – preferable for chronic treatment (e.g. to avoid taking drug at school).
  3) METHYLPHENIDATE is also available as **transdermal patch**.
- initiate at lowest available dosing once daily → increase every 3-4 days until response is noted or adverse effects emerge.
- *learning* often is enhanced at low doses, but *behavior* improvement requires higher doses.
- drug holidays should be tried on weekends, holidays, or during summer vacations.
- placebo periods (for 5-10 school days) - to determine whether drugs are still needed.
- adverse effects: anorexia and growth suppression (growth curves should be followed!!!), sleep disturbances, mild anxiety, rebound (e.g. posttherapeutic agitation, anger, lethargy); most individuals develop tolerance for adverse effects within few weeks (but tolerance does not develop to neurotransmission augmentation of ADHD-related neurochemistry).
  N.B. stimulants, particularly METHYLPHENIDATE, have some risk for sudden death!
- contraindications - narrow-angle glaucoma, hypertension, MAOI use, advanced arteriosclerosis, hyperthyroidism, motor tics (questionable! – tics are not CI in most guidelines) or Tourette syndrome (for "–phenidates").
  – BP improves in some individuals with hypertension, whereas others simply need slight increase in antihypertensive dose.
  – tics may improve or worsen.
- children should be screened for heart problems with ECG before getting "–phenidates".
- spectrums of therapeutic efficacy and adverse effects of all psychostimulants are similar, but for individual, therapeutic efficacy may vary greatly among drugs, preparations, or formulations (generic vs brand name).

  Typically, 1/3 of ADHD patients do not respond / cannot tolerate this class of agents!

  Nonresponders to one stimulant should start another stimulant trial; if two stimulant trials are unsuccessful → try second-line agents

NONSTIMULANTS

- second-line agents; no abuse potential!

FDA approved:

1. **ATOMOXETINE** (Strattera) - selective norepinephrine reuptake inhibitor (SNRI)
   – effective in ADHD (may be used as alternative or adjunct to stimulants).
   – 5-10% patients are poor metabolizers → increased drug exposure.
   – cases of *reversible hepatic failure* have been directly attributed to atomoxetine.
   – contraindications: use of MAOIs within 2 wk, narrow-angle glaucoma.

2. **GUANFACINE extended-release** - relatively selective central α-2A adrenergic agonist – enhances (!) norepinephrine tone in prefrontal cortex (the way stimulants work) - ultimately enhances working memory.
   – highly tolerable and safe drug.
   – helpful in treating pediatric *hyperactivity*, tics.
   – reduced BP and reduced heart rate commonly appear upon drug initiation, along with somnolence, sedation, and fatigue, which tend to diminish over a 2-week period.
   – may be used cautiously (risk of ventricular fibrillation) with stimulants.
   – CLONIDINE is also central α-agonist but much less selective than GUANFACINE.

Antidepressants (IMIPRAMINE, DESIPRAMINE, BUPROPION, VENLAFAXINE) – helpful as adjunctive.

No-efficacy:

MODAFINIL in August 2006 received no-approval letter from FDA for treatment of ADHD!

ST. JOHN'S WORT - not more effective than placebo.

BIBLIOGRAPHY for ch. "Psychiatry" → follow this LINK >>