Complex and coexisting conditions in ADHD

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Differentials & Additionals: CD, BP, ASD, Scz, LD, Ep, SUD

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No competing financial interests
Other symptom patterns coexist

- Conduct/oppositional disorders
- ADHD
- LD
- PDD
- DCD
- Tourette
- Anxiety & depression
- Epilepsy; S/U
- Schizophrenia

FraX; TS; 22q11
Differential diagnosis

- Non-hyperactive behaviour problems
  - Insomnia; oppositionality; tantrums
- Other types of overactivity
  - Stereotypy; Tourette; agitated; catatonic; manic
- Other types of inattentiveness
  - Intellectual handicap; specific learning disorder
- Other types of disinhibition
  - Reactive attachment disorder; frontal; autistic

and all these can coexist with ADHD; recognise disorganised pattern
Overlap of hyperactivity and conduct disorder

- Information comes from
  - Neurodevelopmental associations
  - Twin studies
  - Longitudinal course and prediction
  - Drug response

Does the distinction affect treatment?
Hyperactivity & conduct disorder

Effect size of methylphenidate

Score in SD units on total disruptive scale

ADHD

Conduct disorder

Cases from a clinic sample of boys referred because of disruptive behaviour: Psychol Med 1987
Hyperactivity & conduct disorder

Effect size of methylphenidate

Cases from a clinic sample of boys referred because of disruptive behaviour: Psychol Med 1987
Direct and mediated continuities in ADHD

fMRI & PET changes persist
Direct and indirect continuities in ADHD.

- Genes for combination: COMT
- Continuing dyscontrol
- Mediators – harshness; peer rejection; substance misuse? academic failure?
Conclusions on HA/CD

- Not usually “comorbidity”; CD is a mediated complication

- ODD/CD can be a differential; identify inattention

- Mixed HA/CD is like HA in neurodevelopmental changes and drug response

* Modify mediators
* Consider addition of drugs reducing aggression eg aripiprazole/ risperidone
ADHD and Affective Change

- Sometimes anxiety results from failure
  - (not found in longitudinal research)
- Sometimes “affective” may be ADHD
  - volatility, overreactiveness, dysregulation
- Sometimes “ADHD” means agitation
- Sometimes anxiogenic environment comes from ADHD parents
- Linked causes (5HT genes; pregnancy stress)

*Stimulants less effective, not contraindicated; SSRIs of value but NB activation; consider NA drugs, pregabalin*
ADHD and attachment disorder

- Attachment pattern: Only Type “D” is associated

- Attachment disorder: disinhibited type is a differential diagnosis - (social v general; ambivalence; shallow relationships; not inattentive)

- Attachment history: does not predict treatment response
### Bipolar children? Controversial redefinition of chronic mood upset

<table>
<thead>
<tr>
<th>Typical adult</th>
<th>Severe adult*</th>
<th>“Pediatric BPD”**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mania or MDD</td>
<td>Mixed 40%</td>
<td>Mixed 55%</td>
</tr>
<tr>
<td>2–8 months discrete</td>
<td>Continuous, rapid 20%</td>
<td>Continuous, rapid 77%</td>
</tr>
<tr>
<td>Treatment Responsive</td>
<td>Resistant</td>
<td>? Resistant</td>
</tr>
</tbody>
</table>

What is the supposed phenomenology of mania in children?

- Irritability
- Euphoria
- Grandiosity
- Hypersexuality
- Racing thoughts
- Insomnia
- Overtalkative, distractible, increased activity
## Cardinal features of mania

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
<th>Specificity</th>
<th>Impairing</th>
<th>Look for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoric</td>
<td>++</td>
<td>+++</td>
<td>( +)</td>
<td>- Substance use; medication; epilepsy</td>
</tr>
<tr>
<td>Irritable</td>
<td>+++</td>
<td>(+)</td>
<td>+++</td>
<td>Episodicity; mood context; -provocation</td>
</tr>
<tr>
<td>Grandiose</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>Fluctuations; inappropriate; -arrogance</td>
</tr>
</tbody>
</table>
## Associated features of mania

<table>
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<th>Look for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>+++</td>
<td>-</td>
<td>( +)</td>
<td>CHANGE of activity</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>+</td>
<td>(+)</td>
<td>+++</td>
<td>- Abuse</td>
</tr>
<tr>
<td>Insomnia</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>Change; no daytime fatigue</td>
</tr>
</tbody>
</table>
What phenomenology is useful in diagnosing mania in children?

- Irritability
- Elated mood
- Grandiosity
- Hypersexuality
- Racing thoughts
- Insomnia
- Overtalkative, distractible, increased activity
- Episodicity
How long must an episode be?

20% of bipolar NOS converted to bipolar I or II after 2 years.

1-2 days recommended as minimum length of episode; otherwise regard as emotional dysregulation until better evidence comes.

Clinical Implications

- Important to recognise bipolar disorder in childhood
  - predicts a poor outcome
  - delayed treatment worsens prognosis (?)
  - guide to therapy
  - caution with antidepressants
  - caution with stimulants

- Important not to over-recognise
  - require episodes of more than 1-2 days
  - avoid nonspecific use of neuroleptics

- Differential diagnosis required
  - consider alternative diagnoses
  - bipolar disorder may co-exist with other problems
Treating mood disorders in ADHD

- **MANIA**
  - Explain; ensure safety; ?admit; avoid stimulants
  - Lithium, divalproate, neuroleptics; +#2 at 8 weeks

- **DEPRESSION**
  - CBT; stabiliser or SSRI [avoid manic switch]
  - Consider continuing prophylaxis

- **MOOD DYSREGULATION**
  - Control ADHD; social interventions; ?risperidone

Around 30% of ADHD boys show autistic symptoms*

**Cross-trait correlations**

DZ

Approx 50% of genetic influences are common to both disorders¶

MZ

Clarifying ‘comorbidity’: ADHD in one twin predicts autism in the other.

Approx 50% of genetic influences are common to both disorders.


Cross-trait correlations

DZ

MZ

Communication
ADHD and autism

- Apparently two distinct problems
  - independent actions of stimulants
  - additive neuropsychological changes
- Sometimes an autistic overactivity
  - Overactivity in autism more likely to be repetitive
  - “hyperkinesia with stereotypies” barely exists
- Sometimes a iatrogenic link
- Coexistence often due to linked causes

Stimulants, risperidone, aripiprazole & sertraline are best established medicines; behaviour therapy effective for challenging behaviour.
Substance Misuse: ADHD & SUD

ADHD

Genes

Toxins

CD

Adversity

SUD
Do stimulants cause SUD?

- IV or inhaled MPH is addictive
- Oral MPH, especially XL, causes little euphoria
- Diversion well known, especially in universities (30-50p per tablet)
- Wilens (2003): meta-analysis indicates protection (OR 1.9)
- Huss (2008): MPH delays onset of regular nicotine use
- MTA (2008): behaviour therapy protective, not MPH
Managing SUD in ADHD

Confidential, non-judgemental interview

Recognition of other problems (inc. gangs)

Education, esp. skill-based & peer-driven

RCTs suggest medication not useful

MST, FFT, motivational interviewing
Managing ADHD in SUD

Establish form, sequence, episodicity

Stimulants not contraindicated by alcohol/cannabis

Monitor use & effect of stimulants closely

Avoid immediate-release

Consider atomoxetine, bupropion, lisdexamfetamine

Medications not indicated for the SUD
ADHD affects about a third of children with epilepsy

175 children with ep (90 males; age range 9 to 14 years):

20 met DSM-IV criteria for ADHD combined type;
42 ADHD, predominantly inattentive type;
4 ADHD, predominantly hyperactive-impulsive type.

Sex, seizure type, and focus of discharge were not predictors of ADHD

Dunn DW et al 2003  Dev Med Child Neurol 45: 50-4
National Health Interview Survey 1988

<table>
<thead>
<tr>
<th></th>
<th>Seizures N=121</th>
<th>No seizures N=3,950</th>
</tr>
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<tbody>
<tr>
<td>ADHD</td>
<td>28%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Antisocial</td>
<td>18%</td>
<td>8.8%</td>
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McDermott et al 1995 J Ep 8 110-118
National Health Interview Survey 1988

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<tr>
<th>Condition</th>
<th>Seizures</th>
<th>No seizures</th>
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<tbody>
<tr>
<td>Active and inactive equally affected</td>
<td>N=121</td>
<td>N=3,950</td>
</tr>
<tr>
<td>Clumsiness and learning disability predict ADHD</td>
<td>28%</td>
<td>4.9%</td>
</tr>
<tr>
<td>ADHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family background moderates little Antisocial</td>
<td>18% (authors’ interpretation is via family reaction, which seems challengeable)</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

McDermott et al 1995 J Ep 8 110-118
Possible brain mechanisms for ADHD in epilepsy

Linked risk factors: genetic, environmental

Impairment of attention by epilepsy
  absences, TCI, nocturnal CSWS, microsleeps

Impact of seizures on broader mental function

Underlying neurological changes; (ADHD often present first)

Adverse effects of antiepileptics; or of noncompliance
Survey of Newly Diagnosed Unprovoked Seizures

<table>
<thead>
<tr>
<th>Before first seizure:</th>
<th>Cases N=109</th>
<th>Controls N=218</th>
</tr>
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<tbody>
<tr>
<td>ADHD</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>ADHD (I)</td>
<td>6.4%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Hesdorffer et al 2004 Arch Gen Psychiat 61 731-736
Anticonvulsant effects

300 children on anticonvulsants for epilepsy:

phenobarbitone: 76% conduct problems (esp. ADHD)
other anticonvulsants: 31%

Domizio S et al 1993 Childs Nerv Syst 9:272-4

Warning signs: High levels, low folate, polypharmacy

To Note: Irritability, sedation, aggression

Beneficial effects: via seizure control & mood stabilisation

Titration: use well-recorded monitoring
Methylphenidate in epilepsy

Gucuyener K et al Child Neurol  2003 18(2):109-12
57 ADHD + seizures  ADHD + EEG better; seizures unchanged
63 ADHD + EEG change

30 ADHD + epilepsy  ADHD improved no fits in seizure-free
3/5 with seizures worse

Feldman et al 1989 Am J Dis Child 143(9):1081-6
10 ADHD + epilepsy  ADHD improved no fits in seizure-free

30 brain injury + fits trend to fewer seizures
Linzi

Linzi, age 7 years, was adopted at age 3 months from a biological family in which her mother had been institutionalised for schizophrenia for 2 years at the time of the birth, and the father was an inmate of the same hospital with probable schizophrenia.

Linzi’s early temperament was difficult and intense, but her adoptive parents coped well. At school, however, she has struggled. Her concentration is very poor and she is very restless and impulsive, to the extent that the other children shun her and the school is planning to exclude her. On evaluation, IQ is 106, she can’t read at all, she’s not clumsy, but very distractible and has to be kept firmly on task.
ADHD and schizophrenia

- Is she at risk for schizophrenia?
- If so, is this a contraindication to methylphenidate?
- What are the hazards of withholding methylphenidate?
- Balance of risk and benefit?
ADHD and Tourette disorder

- Possible common causes
  - Conflicting genetic findings; ADHD is not more common in relatives of TD probands, but is more common in relatives who have TD
- Sometimes a iatrogenic link
- “Overactivity” may be multiple tics
- ADHD predicts poor adjustment in TD

Stimulants do not cause TS but may increase tics in 10%; consider atomoxetine; can add clonidine or neuroleptic
Underactivation in functional MRI

Diminished activation in tests of inhibiting response
Functional MRI in adults with Tourette disorder

Increased activation of “inhibitory” circuits during voluntary suppression of tics

*Peterson et al (1998) Arch Gen Psych 55 326*
Medical treatment in “comorbidity”

- Mental retardation
  As in simple ADHD; more AEs; enhanced monitoring needed
- Autism spectrum
- Coordination problems
  Treat but add
- Conduct disorders
- Anxiety
  Predicts poor response but not contraindicated
- Tourette
  Nonstimulants sometimes needed
- Bipolar disorder
  Caution ++ in BP I or II; stimulants in “PBD”
- Epilepsy
  Stimulants are not contraindicated and may be useful
- Attachment disorder
  Differentiate pattern; cause does not determine response