ADHD IN FEMALES

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ATTENTION DEFICIT HYPERACTIVITY DISORDER: CHARACTERISED BY...

At an extreme of:-
- Inattention (or distractibility)
- Impulsivity
- Hyperactivity

and -

PREVALENCE & ONSET

- 4% to 6% of children (varying across countries)
- 2% to 4% of adults (persisting forms)
- Ratio male to female roughly 3:1 in childhood, but close to 1:1 in adulthood - may reflect under-recognition, later onset, or remission in males (or all three)
- Evidence for expression of symptoms in early adolescence to early adulthood (Solanto 2017)
- Inattentive 2.6%, Hyper/Impulsive 1.5% Combined type 1.3%
- (Anecdotal) H/I & Combined 2.8% expressed emotional dysregulation
- ASD about 0.015%, FASD between 0.07% and 14%
Inattentive Sub-type
- Daydreamers
- Not willing to take risks and easily discouraged
- Shy
- Easily overwhelmed
- May be under active
- Self-blaming
- Anxious and depressed
- Anxiety around school performance

Hyperactive/Impulsive sub-type or combined
- Hyperactivity may be expressed in being over-talkative
- Fidgety
- Bossy
- Risk taking
- Unable to keep up with work load
Other traits:
• Problems with times of transitions - between schools, puberty
• Immature (as perceived by others)
• Unable to read other’s cues
• May not have friends
• Difficulty fitting in

*Internalised Symptoms*
WHY THE DIFFERENCE?

• Social & environmental factors
  • Different presentations (but why?), different expectations, different peer pressures

• Genetic and developmental factors
  • Different developmental trajectories, different hormones?, different brains?

• Misdiagnosis: co-morbidities, look-alikes and overlaps
  • ADHD or ASD, BPD, cPTSD, FASD or more than one
ENVIRONMENTAL FACTORS IN CHILDHOOD

- **Females** tend to exhibit inattentive type behaviours rather than disruptive hyperactivity like those horrible boys, hence less noticed; also...

- Behavioural expectations & interpretations by parents & teachers - the “daydreamer”, “chatty girl”, “Dramatic”- considered “acceptable” behaviours or “character traits” (Carbonneau et al 2021)
CHILDHOOD SOCIAL FACTORS

- Socialised into **internalising** problem behaviours, - low self esteem, anxiety & depression, instead of externalising behaviours - aggressiveness, defiance, delinquency

- “**Masking**” of unacceptable behaviours to ensure social acceptance within their peer group (hence confusing friends, teachers & parents alike) (Quinn & Madhoo 2014)

- ...give rise to under-recognition and under referral & hence under-diagnosis (Young et al 2020, Skogli et al 2013)
• Discredited dimorphism...

Highly heritable (70% - 90%): evidence of 12 associated genes with 3 candidate genes (Demontis et al 2019), and 24 “Hot” genes (Yadav et al 2021)

The FOXP2 gene is associated with speech and learning: females show accelerated development in childhood

The relative accelerated development of females in childhood across a number of domains may mask or be protective of symptoms (Quinn & Mahdoo 2014, Mahone 2012), but also indicate a higher threshold of gene & environment to show symptoms (Young et al 2020)
GENETICS, PUBERTY & FEMALES

- Striatum dopamine D1 & D2 receptor density in males is higher than in females across the developmental period, & this may explain a relative over-expression of the hyperactive/impulsive symptoms of ADHD in males (Andersen & Teicher 2000, Williams et al 2021).

- But...
Increasing levels of oestrogen following menarche lead to proliferation of Dopamine receptors in females, but no increased dopamine, with a corresponding increase in symptoms.

Male Dopamine receptor density peaks before and during puberty with pruning leading to the evident decline in symptoms leading into adulthood (particularly in hyperactivity/impulsivity).

This may explain the relative increase in the proportion of females to males with ADHD in adulthood (Nussbaum 2012) and contribute to an apparent late onset (Ostojic & Miller 2016).
• Males and females with ADHD display greater numbers of high risk behaviours across the transition from childhood to adulthood than their neurotypical peers

• Greater risk of STDs, and young or unplanned pregnancies (cf self-identity issues). (Rokeach et al 2018, Isaksson et al 2017)

• Increased risk of developing a Substance Use Disorder, with females more likely than males to develop alcohol and cannabis abuse (Fuller-Thomson et al 2021)

• Both males and females with ADHD are at a higher risk of developing an Eating Disorder (Young et al 2020).
HORMONES...& LIFETIME TRAJECTORY

- The effects of gonadal hormones on ADHD are significantly understudied, though the effects on cognitive function are better understood.

- Contemporary research, based on self-reports, cautiously shows higher rates of PMDD and PND, and more severe menopausal symptoms, in women with ADHD (Dorani et al. 2021)

- Depression and anxiety have earlier onset and longer episodes with greater rates of suicidality in women with ADHD (Fuller-Thompson et al. 2016), and this may divert attention from ADHD (Antoniou et al. 2021) - (Occam’s Razor?)
ADHD ACROSS THE MENSTRUAL CYCLE

- ADHD symptoms increase as estradiol decreases and progesterone (or testosterone) increases: may also be related to decreased effectiveness of medication

- Most evident changes in symptoms in early follicular & early luteal phases

- More evident in women with high trait impulsivity (as in Hyperactive/Impulsive Sub-type) (Roberts et al 2018)

- Medications for co-morbidities may interact with ADHD medications to cause reduced effect in the luteal phase
MIGRAINES...& CLINICAL SUSPICION

• Migraine is experienced by 16% to 18% of females & about 6% of men in the general population

• Migraine is found in **26%** of those with ADHD with the incidence **higher in females** than males (Kutuk et al 2018), & more likely in those with more severe symptoms of ADHD (Hansen et al 2018)

• Recent research indicates a genetic link between ADHD, Migraine and Major Depressive Disorder

• The ADHD - Migraine relationship is stronger in those with Migraines with visual disturbances
OESTROGEN...& MIGRAINES

- Migraines are lower in frequency pre-pubertally compared to post-pubertally.
- The risk of migraine increases by a third around the commencement of menstruation, with falling oestrogen levels (Verrotti et al 2020).
- Progesterone appears to be protective, with frequency of migraines lower in the earlier luteal phase.
• Women with ADHD may be more vulnerable to Menopausal Depression through changes in serotonin (but also the physical changes)

• Lower levels of oestrogen may lead to reduced levels of dopamine and hence less response to ADHD medications and more marked symptoms
UNWELCOME OUTCOMES?

- ADHD is linked to **twice** the rate of premature mortality across the population (Faraone 2015)

- Significantly higher in females with ADHD & associated with “Problems with self-concept” (Kakuszi et al 2018)

- Under-diagnosis of females leads to under-treatment in comparison with males & hence greater risk from impulsive or distracted behaviours

- This may explain the greater rate of premature mortality secondary to accidents (of all kinds) in females with ADHD versus males with ADHD, even adjusted for comorbidities.
CO-MORBID CONDITIONS AND LOOK-ALIKE

“LOOKS LIKE A DUCK, QUACKS LIKE A DUCK” ... BUT IS ACTUALLY A GOOSE
A MASTER OF DISGUISE: ASD & ADHD

- Genetic overlap

- ADHD co-morbid in as many as 40% - 70% of children with ASD and 16% adults with ASD

- ASD co-morbid in 12% to 25% youths with ADHD (Antshel et al 2016)

- Significantly skewed towards males 5:1 in childhood, but 2:1 in adult clinics...why?
SYMPTOM OVERLAP & DIFFERENCES

ASD symptoms do not occur without ADHD symptoms (Antshel et al 2016):

- Motor dysfunction (eg hyperactivity, impulsivity)
- Externalising behaviours (emotional outbursts, aggression)

...but there are differences:

- ASD - impaired planning and shifting attention
- ADHD - impaired behavioural inhibition and sustaining attention
ASD IN FEMALES...

- Assessment tools & criteria are largely based on research and validation in males - hence less suspicion because...

- **Unrecognised** through lack of understanding of ASD in females:
  
  - “Four to five years of depression and anxiety treatment...years of talking therapy...and not once did anyone suggest I had anything other than depression”.
  
  - “I’ll always remember my special needs teacher saying I’m too poor at maths to be autistic.”
  
  - “There’s potential for you copying a guy’s flirtatious behaviour without realising that’s what you’re doing.” (& hence prevalence of sexual abuse)
...AND, LIKE ADHD, DISMISSED AS “FEMALE BEHAVIOUR”:-

- **Masking**: “Many women described actively learning how to ‘mask’ from different media sources including characters on television, magazines, books on body language and novels:

  “They’d have the right behaviour for certain things, so ‘If you want this, you should do this’.”

- **Passivity** in females:

  “The reward for trying hard to be normal was to be ignored because you were acting normal and I look at stories online of kids who were going off the rails and I think, I should have just burnt more cars”

- **Social group** pressures:

  “...some women reported that their experiences of peer rejection left them ‘desperate’ for acceptance, which in turn made them more vulnerable to exploitation” ...”many women reported finding it difficult to ‘read’ other people’s intentions, and so struggled to understand if a man was just being friendly or was sexually attracted to them.” (Bargiela et al 2016)
ARE THEY DIFFERENT?

- ASD & ADHD: two conditions with distinct genetics and environmental factors, with distinct but similar symptoms
- ASD/ADHD: two conditions with closely overlapping genetics and environmental factors, with overlapping symptoms
- ASD: one condition with distant overlapping genetics with ADHD displaying some symptoms that look like ADHD
- & the answer in October 2022 is....all three! (Mattheisen et al 2022)
ADHD & BPD/cPTSD

Overlapping symptoms
ADHD & Borderline Personality Disorder

BPD
- chronic suicidality
- emptiness
- non suicidal self injuries
- frequently PTSD
- dissociation

ADHD
- disorganization
- hyperactivity
- deficits in executive function
- attentional deficit
- impulsive behavior

ADHD & Emotional Regulation In Adults
Alexandra Philipsen
Department of Psychiatry and Psychotherapy,
University Hospital Bonn, Germany
• Borderline Personality Disorder (BPD) and Complex Post Traumatic Stress Disorder (cPTSD) share **genetic vulnerability** to the effects of trauma, and share trauma as an **environmental trigger** in their development (Weiner et al 2019, Jowett et al 2020, Calvo et al 2020).

• **ADHD** shares **genetic factors** with **BPD** and early life trauma can be a factor in development of ADHD (Distel et al 2011, Ditrich et al 2021).
• Emotional Dysregulation, Impulsivity and Interpersonal impairments are overlapping, look-alike symptoms across all three disorders.

• Co-morbidity of ADHD and BPD is high, as much as 1/3 in some studies, with the ADHD combined form being the most severe due to the expression of overlapping symptoms having a wider range of effects. (Rufenacht et al 2019)
Emotional Dysregulation:-

- **BPD** - self injury and suicidality, unstable & negative emotional response to environmental stimuli (often interpersonal) with poorer mentalising capacity, slow return to baseline. Overuse of ruminative and “blaming others” strategies

- **cPTSD** - reactive anger & substance abuse, feelings of shame, guilt or worthlessness. Suicidal thoughts. Feeling “cut off” from people. (Jowett et al 2020)

- **ADHD** - unstable & negative emotional state, slow return to baseline. Overuse of ruminative and “blaming others” strategies - but less intense and not as central to disorder as in BPD. (Rufenacht et al 2019)
• **Impulsivity:**

• **Motor or behavioral impulsiveness:** acting without thinking or on the spur of the moment – aADHD>>BPD
  Eg impatience, butting in

• **Attentional impulsiveness:** difficulty focusing on a task at hand (easily distracted by other things) – aADHD>>BPD

• **Non-planning impulsivity:** present-moment focus without regard for future consequences – BPD>>ADHD
  Eg stressful interpersonal situations, self harm (Weiner et al 2019)
Interpersonal impairments in BPD:

- Reflecting past trauma - driven by fear of abandonment, emotional dysregulation and impulsiveness giving rise to (Euler et al 2021):
  - difficulties in trusting others,
  - patterns of over-involvement (intrusive, emotionally demanding)/withdrawal (aloof & hostile)
  - idealisation (you’re my hero)/devaluation of relationships (I want to kill you)
Interpersonal impairments in ADHD:

- Driven by behavioural impulsiveness:
  - chattering, interrupting others talking, intruding into other’s activities

- Driven by attentional impulsiveness:
  - inattentive “aloofness” or indifference – “I’m not ignoring you, just distracted by something else”
  - poor conflict resolution – “What’s the problem?” and “It’s your fault”
TREATMENT: MEDICATION TO MINDFULNESS

- Medication and non-pharmacological interventions can be effective in adult ADHD but must be tailored to the individual’s mental and physical conditions.

- Medications for mental and physical co-morbidities may interact synergistically or antagonistically with ADHD medication (& each other).

- Female hormonal variations affect both symptoms and medications.

- Psycho-social factors may make non-pharmacological interventions more readily sought by females than males (Liddon et al 2018)
A CLINICAL VIGNETTE

- OJ is a 21yo caucasian woman with diagnoses of ASD, BPD, PMDD and ADHD,
- Commenced Zoely in continuous dosing for PMDD with benefit, but still with some emergence of symptoms in the immediate pre-menstrual phase.
- Commenced on lamotrigine for affective dysregulation considered to arise from her BPD with excellent effect and an ensuing positive engagement with DBT.
- Commenced on venlafaxine at the same time as the lamotrigine and Zoely but felt it ineffective and worsening her symptoms.
- Subsequently diagnosed with ADHD: Lisdexamfetamine very effective but with a reduced effectiveness also noticed pre-menstrually.
OJ’S DILEMMA

• Zoely had benefit for PMDD; however, lamotrigine and estradiol mutually reduce each others effectiveness (via metabolic pathways)

• Antidepressants appear to reduce estrogen levels (Pavlidi et al 2021)

• This may explain the breakthrough of PMDD symptoms and reduced effectiveness of Vyvanse in controlling ADHD symptoms, which themselves will be more evident due to lower estrogen.

• However, the lamotrigine is highly effective in controlling affective dysregulation - hence her dilemma!

• Venlafaxine acts synergistically with Vyvanse, increasing risk of serotonin syndrome, but also its noradrenaline component may worsen some symptoms. In the absence of CYP450 gene analysis, this may explain some of OJ’s symptom worsening.
LESSONS FROM OJ

• Check medication interactions

• Consider CYP450 gene analysis in complex clients with multiple medications

• Change one medication at a time wherever possible

• Start low and go slow

• Assume, until shown otherwise, that hormonal variations will affect medications and/or symptoms (Kok et al 2020)
CONCLUSIONS

• ADHD in females is under-recognised & under-treated - with significant negative consequences

• Under-recognition arises from differences in social perceptions of males & females, and from differing developmental trajectories masking symptoms and leading to “later onset”

• Females tend to internalise symptoms, whilst males tend to externalise them

• Hormone cycles have a negative effect on symptoms of ADHD and co-morbid disorders, and may affect medication.
EVERYONE SHOULD HAVE A LOW THRESHOLD OF SUSPICION FOR ADHD IN FEMALES WITH:

- Trauma in childhood
- Depression/Anxiety/Affective Dysregulation
- Low self esteem or interpersonal issues
- Substance abuse
- Eating Disorder
- PCOS
- Hormone driven variation in Migraine & any of the above
QUESTIONS?
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BRAIN TRAINING

- Behaviour and brain structure are malleable (“neurons that fire together, wire together”)

- Impairments in attention & planning, for example, are moderated through structured behavioural interventions (Jonsson et al 2021)

- “ADHD Training” is really available & effective: routine establishment, priority management, time management, stress management and self esteem management (Gutman et al 2020)

- Mindfulness training is shown to be useful (Poissant et al 2019)

- Game based interventions may also be useful (Ahufinger 2021)
UNWELCOME OUTCOMES - DOUBLE THE RISK WITH ADHD & ASD

- Suicide in those with ADHD and ASD:
  - “Rational Pragmatism” +/-
  - “Existential ennui” +
- Impulsivity, Emotional Dysregulation and Impaired Foresight =
- High Risk...very high risk.
ATTENTION DEFICIT HYPERACTIVITY DISORDER

- The popular misconception: “Just naughty boys misbehaving”

- The evidence: the most common neurodevelopment disorder, with significant impairments that persist into adulthood for up to half of those with the disorder in childhood (DSM-5)

- Genetic underpinning with environmental trigger(s) and significant co-morbidity with other disorders (Lichtenstein et al 2010, Grimm et al 2018)
DIMORPHISM IS DEAD

"Give me the child for the first seven years, and I will give you the (wo)man"
Jesuit maxim

"Winning is a habit. Unfortunately, so is losing."
-Vince Lombardi

We are what we repeatedly do. Excellence, then, is not an act, but a habit.
- Aristotle

"Go on..."
"Don't..."
"You have to..."
"Do it..."
"I want you to..."
"C'mon..."

Life long Patterns of Thought & Behaviour

Individuals with either ADHD or ASD have a 65% to 90% risk of developing concomitant psychiatric disorders:

- adults with ASD present high rates of co-occurring anxiety, depression, bipolar disorder (BD), and schizophrenia spectrum disorder (SCZ)
- adult ADHD is reported to co-occur with anxiety disorder and major depressive disorder (MDD), BD, personality disorders (PDs), SCZ, and substance use disorder (SUD). (Solberg et al 2019)
**SUICIDALITY**

**ADHD and suicidality**

Individuals with ADHD have increased risk of suicidality:

- Suicide attempts OR = 2.37 (95% CI 1.64-3.43)
- Suicidal ideation OR = 3.53 (95% CI 2.94-4.25)
- Suicidal plans OR = 4.54 (95% CI 2.46-8.37)
- Completed suicide OR = 6.69 (95% CI 3.24-17.39)

*Significantly higher in females & associated with “Problems with self-concept” (Kakuszi et al 2018)*