Behavior and Anxiety in Angelman Syndrome in the COVID-19 Era
Talk Outline

• Review three cases of behavioral challenge
• Research review on most common behavioral problems
• Comments on treatment approach
• Time for questions
## Disclosures – 5 years

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<tr>
<th>Source</th>
<th>Research Funding</th>
<th>Advisor/Consultant</th>
<th>Employee</th>
<th>Speakers’ Bureau</th>
<th>Books, Intellectual Property</th>
<th>In-kind Services (example: travel)</th>
<th>Stock or Equity</th>
<th>Honorarium or expenses for this presentation or meeting</th>
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No treatments will be discussed today that pertain to disclosures
Disclosures

Medications discussed may be “off-label” meaning the medication does not have FDA approval for that specific indication.

I am not promoting or selling any commercial-related items.
Our New Normal?
Case 1: John

- 19 year old man with AS
  - Increased upset with separation from parent
  - Agitation with limit setting (especially around food)
  - Requesting school on a regular basis
Agitation and Aggression in AS

- Higher rates of aggressive behaviors than many other genetic syndromes (Arron et al. 2011)

- Study of 12 subjects with AS found high scores on measures of irritability on ABC-irritability subscale (Wink et al., 2015)
Data from Natural History Study

301 Subjects with AS recruited over 6 study sites over 8 years

High rates of aggressive behaviors reported

Higher rates among UPD/ImpD and UBE3A populations

Higher scores on measures of irritability with age (biggest effect in UBE3A)

<table>
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<tr>
<th>Behavior</th>
<th>Deletion % (N = 211)</th>
<th>UPD/ImpD % (N = 56)</th>
<th>UBE3A % (N = 33)</th>
<th>Total % (N = 300)</th>
<th>Difference in genotypes (p value)</th>
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Abbreviations: UPD, paternal uniparental disomy for chromosome 15q11q13; ImpD, imprinting defects that alter expression of the maternally inherited copy of UBE3A.
Understanding Aggression

COMMUNICATION

ANGER

PAIN

LOOK AT ME!!!
Unrecognized Medical Illness

- Constipation
- Dysmenorrhea
- Gastroesophageal reflux
- Dental problems
- Scoliosis
- Post-ictal confusion/sedation.

Many of these conditions are elevated in adolescence/adulthood (Larson et al. 2015)
Functional Behavioral Assessment (FBA)

A Antecedent
A cue to perform a behavior that leads to a reward

B Behavior
Child’s action as a result of the cue

C Consequence
What happens following the response. Reward for the correct response.
Anxiety as a Precipitant for Aggression

- There is preliminary evidence for anxiety being a problem in AS
  - Anxiety first mentioned in seminal 2001 study by Dr. Clayton-Smith
  - Larson et al. 2015: Study of adults with AS: 46% of subjects “showed signs of anxiety”
  - Concerns of anxiety increasing into adulthood (Prasad et al. 2018)
  - Parents concerned about anxiety in AS describe aggression most common (ASF funded study)
Recent study assessment tool

- Significant overlap with recent study of 100 subjects with AS with mixed ages
  - High rates of separation distress behaviors (rates among teenage subjects approaching 80%)
  - Most common behaviors:
    - Clingy
    - Not able to relax
    - Nervous habit
    - Trembling
      - Fight or flight

Wheeler et al. 2019
Buspirone treatment case series

- Retrospective case series
  - Three adult subjects with AS who took buspirone for “anxiety behaviors”
  - Reduced self-injury/aggression, calmer, resolved sweating, decreased fear of crowds, reduced excessive swallowing/vomiting
  - First treatment report for behaviors concerning for anxiety in AS
Treatment approach (non-medications)

- Occupational therapy focused on identifying calming sensory interventions
- Augmentative Alternative Communication strategies
  - Requesting “Breaks” or preferred items
  - Visual Schedule
- Behavioral Therapy
  - Help identify precipitants
  - Helpful for tracking response
  - Watch for initial worsening prior to improvement
- Evaluation for medical contributors
- Psychological Therapy:
  - Gradual exposure to fearful stimuli (eg separation)
Treatment Approach (medications)

• Buspirone: Effects on serotonin (serotonin receptor 1A partial agonist)

• Less Severe
  – Benzodiazapines: Effects on GABA (gamma-aminobutyric acid)
  – Selective Serotonin Reuptake Inhibitors and Mirtazapine: Antidepressants, effects on serotonin
  – Propranolol: beta blocker medications, effects on beta 1+2 adrenergic receptors

• More Severe
  – Antiepileptic Medications: Topiramate, lamotrigine, clobazam, gabapentin
  – Antipsychotic Medications: Quetiapine, risperidone, aripiprazaole

Mirtazapine: Hanzlik et al. 2020
When to consider pharmacotherapy

- Lack of improvement with behavioral treatments
- Concern of safety at home or with siblings
- No amount of preparation can make a community trip safe
- Not eligible for day programs or in home care staff due to safety concerns
- Not safe to place any demands
Case 1: John, revisited

- Worked with school BCBA
- Hired in home staff for planned separation
  - Less expectation for constant
- Day schedule enriched for preferred activities
  - Less aggression
  - Plateau in skills
- Low dose buspirone
Case 2: Sam

- 7 year old boy with AS
  - Baseline: constant need to move/explore, easily distracted at school, giddy
  - Less structure with drastic increase in hyperactivity.
  - Constant silly limit testing behaviors and destructive curiosity at home
  - Can’t sit for any prolonged period for online education
Long history of Hyperactivity in AS

Consensus Guidelines for Diagnostic Criteria in AS (Williams et al. 2005)

Table II. 2005: Clinical Features of AS

A. Consistent (100%)
   - Developmental delay, functionally severe
   - Movement or balance disorder, usually ataxia of gait, and/or tremulous movement of limbs. Movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions
   - Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping, or waving movements; hypermotoric behavior
   - Speech impairment, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones

Correlation: Hyperactivity and stress on the parent child relationship (Sadhwani et al. 2019)
Previous evidence for hyperactivity

- Clarke and Marston. 2000: 72 individuals with AS (deletion type)
  - More prominent behaviors related to hyperactivity than control groups
  - Evidence for decrease with age (but may persist into adulthood)

- Berry et al., 2004: 98 individuals with AS
  - Higher rates of hyperactivity as compared to control groups with general developmental delay
Hyperactivity Treatment Approach (non-medication)

• Emphasizing adequate sleep and exercise

• Educational interventions:
  – Movement breaks, minimizing distraction from preferred peers, use of praise
  – Elopement/fall risk

• Occupational therapy:
  – Identifying calming sensory interventions
  – Chewy tubes, hand fidgets to address restlessness
Hyperactivity Treatment Approach (medication)

- Guanfacine + clonidine: Effects on alpha 2 receptors
- Atomoxetine: Effects on norepinephrine
- Serotonergic Medications: Fluoxetine, Amitriptyline (anecdotal experience)
- Antipsychotic medications: Risperidone (severe cases only)
Case 2: Sam, revisited

- Instituted picture schedule
- Enriched schedule for outdoor activity
- Advocacy with school system
- Low dosage guanfacine added and provided mild to moderate reduction in hyperactivity
- Seeking additional therapies outside of school
Case 3: Liz

- 9 year old girl with AS
  - Baseline: Excellent sleep with moderate dose melatonin
  - Now: Taking hours to fall asleep, agitation when left alone
  - Can’t separate from parent at night without tantrum
Sleep Challenges in AS

• High lifetime rates of sleep challenges
• Most prevalent through early childhood but may persist

• Types of sleep problem in one survey (Conant et al. 2009):
  – 72% report difficulty falling asleep
  – 66% reporting difficulty staying asleep
  – 49% reporting reduced total sleep time
Why so Severe?

**Genetic**
- GABA<sub>A</sub> receptor subunits

**Medical**
- Constipation, incontinence
- Seizure, myoclonus

**Behavioral**
- Separation agitation
- Hyperactivity
Separation at Bedtime

Sleep Onset Associations
Behavioral Therapy for Sleep Disturbance

• Strategies to address sleep onset associations:
  – Bedtime Fading
  – Camping out
  – Extinction/Modified extinction
  – “Excuse Me” Drill

• Sleep Hygiene:
  – Consistency
  – Quiet/cool sleep environment

• Training to stay in room safely
Study of Behavioral Sleep Strategy

Five subject trial (ages 2-11 years)

6-8 week period of weekly guidance with Bedtime Fading

Outcome measures: sleep diary and actigraphy

Followed up 1 and 3 months after trial

Results:
- All subjects achieved independent sleep onset
- Marked reductions in disruptive sleep time behavior
- 30 min additional sleep on average each night

Allen et al. 2013
Sleep Disorder Treatment Approach (medications)

- Melatonin: Randomized placebo controlled trial in AS showing efficacy and tolerability (Braam et al. 2006)

- Clonidine: Considered for sleep initiation (Pereira et al. 2020)

- Trazodone: Considered for mid-cycle waking (Pereira et al. 2020)

- Mirtazapine: Case series showing improvement in patients with AS (Hanzlik et al. 2020)

- Quetiapine: May help some with behavioral agitation during the day
Case 3 Liz, revisited

- Parents set consistent bedtime, pushing bedtime back to when patient was sleepy
- Clonidine started to aid some with agitation
- Changing up the parent who helped with nighttime routine
- Maintained consistent wake time with early daytime structure
- Looking into veil beds, room safety assessment
Summary

• Behavioral challenges have exacerbated during COVID crisis

• Parents and clinicians called to be creative, forceful and effective advocates

• Medications play an adjunctive role in overall treatment plan
Questions & Discussion

Thank you!

All questions are good ones.
Citations


