

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



LURIE CENTER

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MASSACHUSETTS
GENERAL HOSPITAL



MassGeneral Hospital
for Children

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

Source	Research Funding	Advisor/ Consultant	Employee	Speakers' Bureau	Books, Intellectual Property	In-kind Services (example: travel)	Stock or Equity	Honorarium or expenses for this presentation or meeting
National Institute of Mental Health (NIMH)	X							
Autism Speaks	X							
Angelman Syndrome Foundation	X							
OVID Therapeutics	X	X						

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)

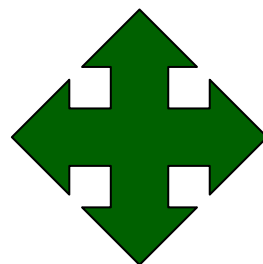
TABLE 2 Percentage of individuals with the specific maladaptive behaviors stratified by genotype at baseline, as reported by parents

Behavior	Deletion % (N = 211)	UPD/ImpD % (N = 56)	UBE3A % (N = 33)	Total % (N = 300)	Difference in genotypes (p value ^a)
Mouthing behaviors	92	89	70	89	.002
Easy excitability	90	91	70	88	.005
Short attention span	89	88	73	87	.069
Fascination with water	79	75	70	77	.486
Hand flapping	68	80	61	70	.111
Hyperactive	69	59	55	65	.155
Frequent laughter	69	54	42	63	.005
Aggressive behavior					
Overall	51	84	70	59	<.001
Biting ^b	27	45	49	33	.012
Hair pulling ^b	44	55	36	45	.161
Pinching ^c	23	43	27	27	.025
Anxiety	19	45	36	26	<.001
Temper tantrums	17	25	52	22	<.001

Abbreviations: UPD, paternal uniparental disomy for chromosome 15q11q13; ImpD, imprinting defects that alter expression of the maternally inherited copy of UBE3A.

Image from Sadhwani et al., 2019

Understanding Aggression

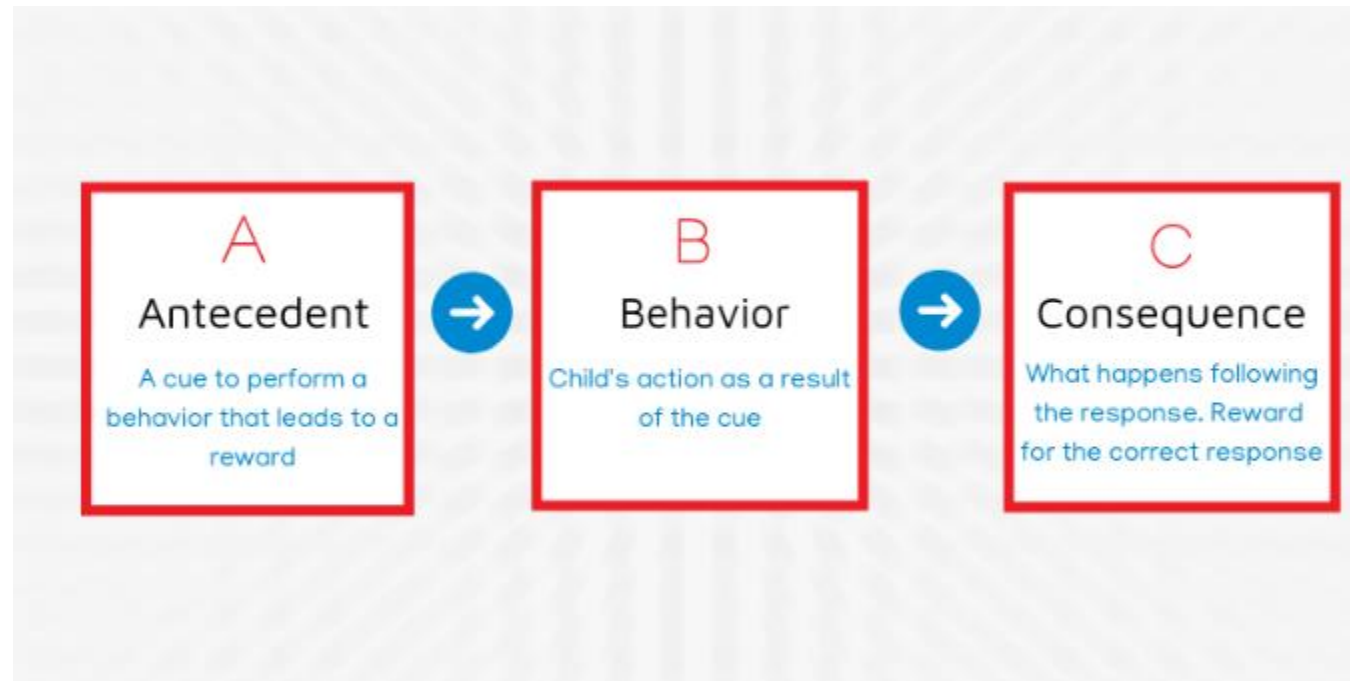


Unrecognized Medical Illness

- 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)

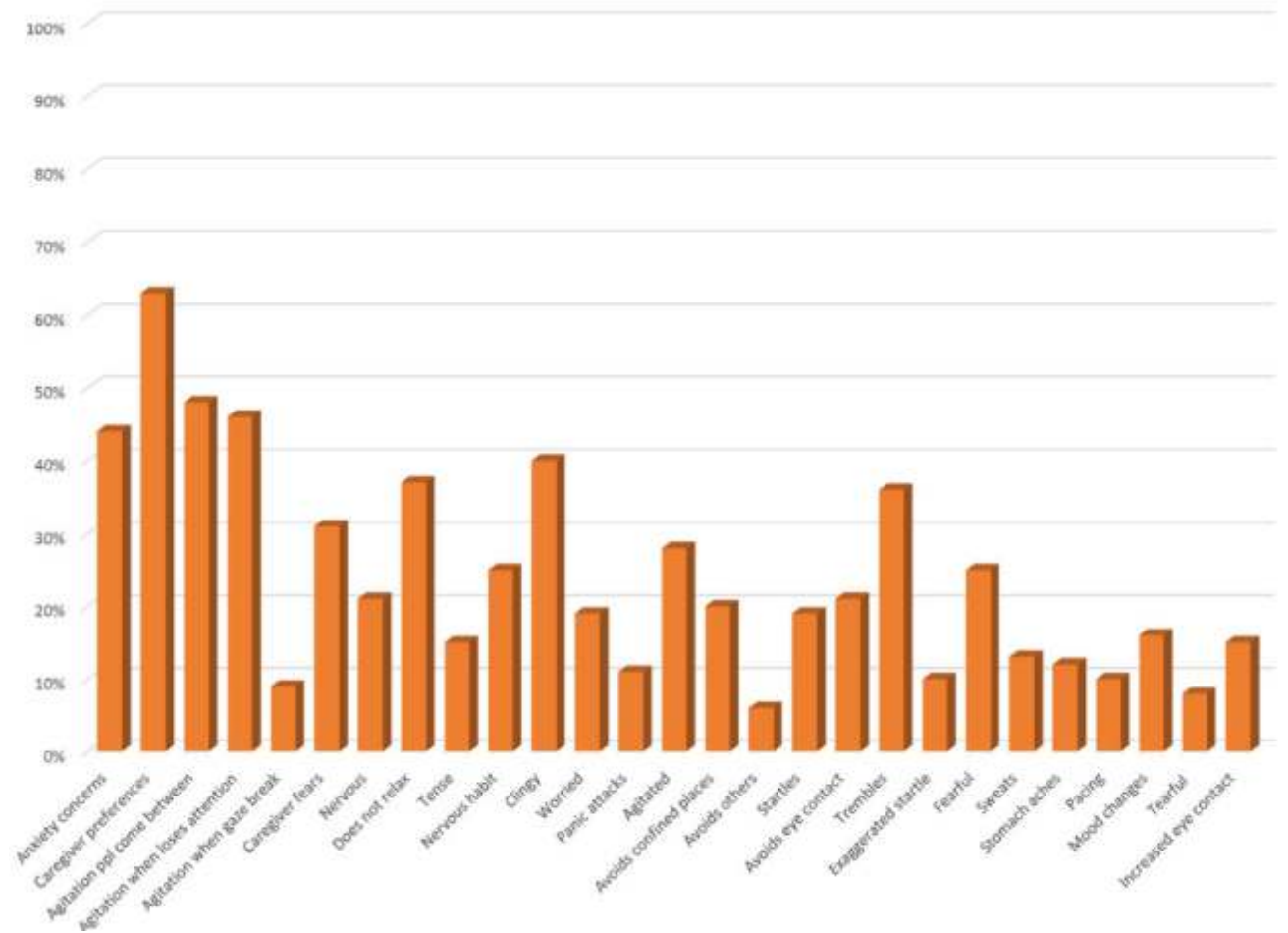


Anxiety as a Precipitant for Aggression

- 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



Bupirone treatment case series

- Retrospective case series
 - Three adult subjects with AS who took bupirone 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, aripiprazole

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 (Sadhvani 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_A receptor subunits



Medical

Constipation, incontinence
Seizure, myoclonus

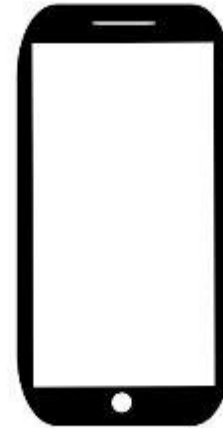


Behavioral

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

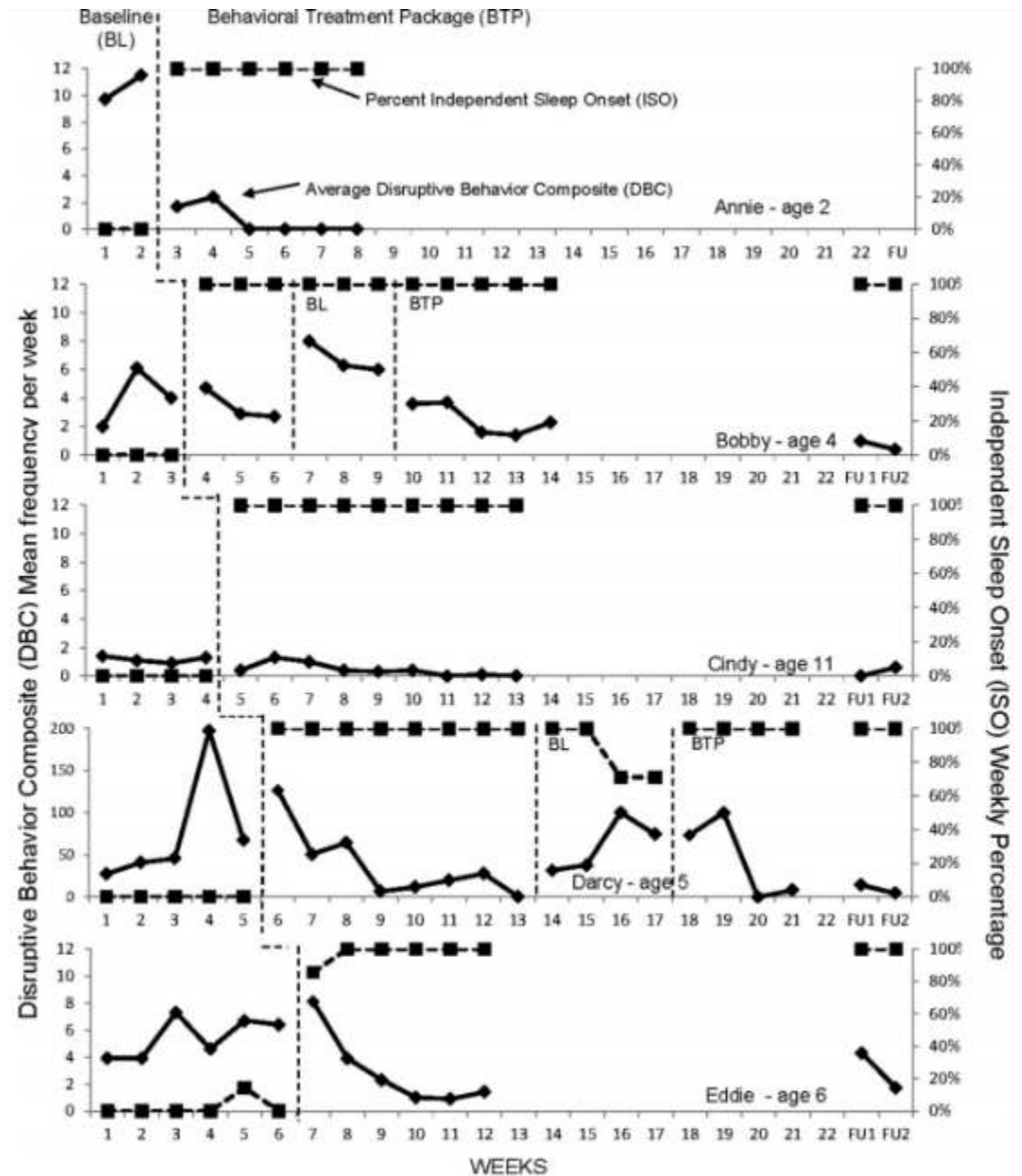


Fig. 1. Disruptive behavior composite (DBC) and independent sleep onset (ISO) for each of the 5 participants. DBC is mean frequency per week (primary ordinate) and ISO is percentage of days per week (secondary ordinate). Follow ups were conducted at 1 and 3 months.

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

Thank you!

All questions are good ones.



MassGeneral Hospital
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Angelman Syndrome Program

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The Angelman Syndrome Program at MassGeneral Hospital for Children, in partnership with the Angelman Syndrome Foundation, aims to provide comprehensive clinical care to individuals with Angelman syndrome.

617-726-6540



Lurie Center for Autism



Care During COVID-19



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