

Psychiatric issues in Children and Adolescents with VCFS/22q11.2 Deletion Syndrome

Kathy Angkustsiri, M.D., M.A.S.
Developmental Behavioral Pediatrics
Medical Director, 22q Healthy Minds Clinic
UC Davis MIND Institute



Center for Excellence in Developmental Disabilities



Disclosures

- None relevant to this presentation
- I am involved in clinical trials in autism and fragile X syndrome for Novartis, Roche, and SynapDx. I do not receive direct salary support for this contracted research.

Childhood Psychiatric Concerns in 22q

- Childhood psychiatric conditions are frequently reported in 22q
- Comorbidities are common
- Considerations include medical conditions, hospitalizations, and developmental delays

Childhood Psychiatric Concerns in 22q

- Attention Deficit/Hyperactivity Disorder (ADHD) 30-50%

- Inattentive, easily distracted
- Impulsive

- Anxiety Disorders: 30-60%

- Specific Phobias
- Separation Anxiety Disorder
- Obsessive Compulsive
- General Anxiety

- Mood disorders (3-11%)

- Depression
- Bipolar disorders

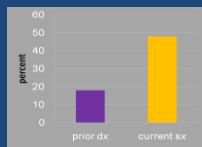
Prevalence of DSM-IV-TR Psychiatric Disorders in Five Age Groups

	Children and Adolescents			
	Children (6-12 Years)		Adolescents (13-17 Years)	
	N	%	N	%
ADHD ^a	161/434	37.10	63/264	23.86
Any anxiety disorder ^b	155/435	35.63	97/286	33.92
Separation anxiety disorder ^d	25/395	6.33	4/259	1.54
Specific phobia ^d	95/433	21.94	48/282	17.02
Social phobia ^d	45/435	10.34	28/286	9.79
Panic disorder ^d	4/333	1.20	2/231	0.87
Posttraumatic stress disorder	1/274	0.36	3/222	1.35
Obsessive-compulsive disorder	24/435	5.52	17/286	5.94
Generalized anxiety disorder	36/435	8.28	30/286	10.49
Anxiety disorder not otherwise specified	1/435	0.23	1/286	0.34
Any mood disorder	15/456	3.29	41/346	11.85
Major depressive disorder ^d	10/456	2.19	31/346	8.96
Dysthymia ^d	5/456	1.10	10/346	2.91
Bipolar disorder or hypomanic episode in children	0/318	0.00	2/317	0.32
Mood disorder not otherwise specified	0/456	0.00	4/346	1.16

Schneider, et al. 2014. 22q Consortium

Psychiatric disorders are underidentified in 22q

- Known psychiatric risk
- CABIL: ~50% have anxiety but only ~20% diagnosed
- Young et al, 2011
 - 12-28% of children with symptoms actually treated
- Tang et al, 2013
 - <50% receive mental health care or medications



Tang et al., 2013

Table 3. Treatment modalities experienced by participants with 22q11.2 deletion syndrome

Treatment mode	All participants	Current psychiatricology	
		Major anxiety disorder	ADHD
Count	112 (100)	47 (42)	35 (31)
Lifetime mental health care	71 (63)	37 (79)**	20 (57)
Current	41 (46)	25 (50)*	13 (31)
Any psychiatric	44 (39)	21 (44)	19 (54)*
Antidepressants and anxiolytics	26 (23)	17 (36)**	8 (23)
Mood stabilizers	7 (6)	4 (8)**	2 (6)
Stimulants and alpha-2 agonists	19 (17)	8 (17)	12 (34)**
Antipsychotics	8 (7)	7 (15)**	2 (6)
Psychiatric hospitalization	8 (8)	4 (8)	2 (6)

Treatments/Recommendations

- Varies based on individual needs

- Behavioral
- Educational
- Medical
 - Labs/procedures
 - Thyroid, calcium, complete blood count, etc.
 - Medications

Considerations

- It is important to determine the symptoms that are most significantly impacting function
 - Generally speaking, there are no “22q specific” medications, but medications should be used carefully with close follow up
 - “Start low and go slow”
- Medications should always be combined with psychological, behavioral and/or educational interventions
- Different children respond differently to medications
- Medical conditions
- Expect changes in dose, medication type...

What’s the target symptom?

- Inattention
- Impulsivity and hyperactivity
- Anxiety
 - Hyperarousal
 - Obsessive compulsive
 - Perseveration
- Mood instability
- Aggression

ADHD treatment

- Behavioral intervention
 - Parent training
- Classroom modifications
- Medications
 - Stimulants
 - Alpha agonists (use with caution if cardiac hx)
 - Atomoxetine (Strattera)
 - Others



Considerations

- Few medications are FDA approved for children under 6 years of age
- Few randomized, placebo-controlled, double-blinded studies have been done in children

Stimulants for ADHD

- Why the concern?
 - Cardiac side-effects
 - Growth
 - Altered dopamine levels in 22q11.2DS due to COMT?



Stimulants in 22q11.2DS

- Gothelf 2004 (4 weeks)
 - 12 children with ADHD
 - Low dose methylphenidate (0.3 mg/kg)
- Gothelf 2011 (6 months) – 0.5 mg/kg
 - 22 children treated
 - No psychotic/manic symptoms
 - Mild elevations in blood pressure
- Conclusion:
 - methylphenidate is effective and usually well-tolerated
 - be aware of side effects and potential risks
 - must weigh risks/benefits with your provider

SAMe in 22q

- S-adenosyl-L-methionine
 - Enhances COMT activity
- 12 individuals with ADHD or depression
- Double-blind, placebo-controlled trial
- 800 mg twice daily

- No differences in ADHD
- No significant side effects
- Small study

Green et al., 2012

Atomoxetine



- Brand name is **Strattera**
 - Functions as a norepinephrine reuptake inhibitor
 - 2nd line medication for ADHD but good for comorbid ADHD and anxiety
- Evidence: Effective for hyperactivity and inattention in 2 RCTs in children with ADHD
- Side effects: increase in heart rate and/or blood pressure, nausea, poor appetite, fatigue
 - Monitoring: growth, heart rate and blood pressure

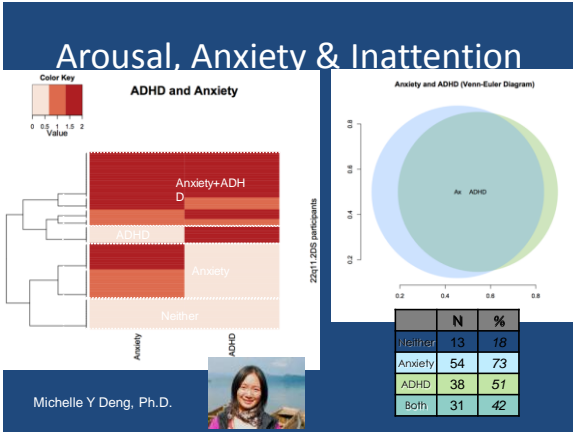
- No clinical trials in 22q

Alpha-2 Agonists

- Clonidine and Guanfacine
- Evidence: effective for hyperactivity and irritability in 2 small RCTs
- Side effects: hypotension, drowsiness
 - Monitoring: heart rate, blood pressure

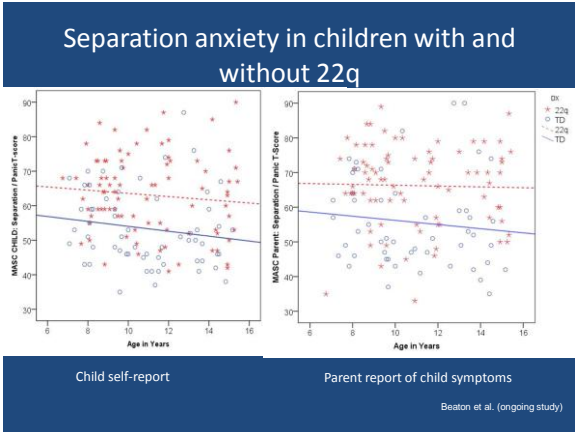
- No clinical trials in 22q





- ## Anxiety in Children
- Many types of anxiety; may present atypically
 - Separation anxiety
 - Panic or tantrums at times of separation from parents
 - Overly clingy
 - Refusing to go to school
 - Extreme worries about sleeping away from home
 - Trouble falling sleep without parents
 - Social anxiety
 - Extreme shyness or social withdrawal
 - Fears of embarrassment or making mistakes
 - Significant worries about peers, school performance, friends
 - Low self esteem

- ## Anxiety in Children
- Obsessive-Compulsive Symptoms:
 - Repetitive thoughts or actions
 - Rituals or Routines that cause stress if not followed
 - Other Symptoms:
 - Worries about things before they happen
 - Resistance to trying new things
 - Panics/overreacts
 - Perseverative questions
 - Seek a lot of reassurance
 - Somatization:
 - Frequent stomachaches and other physical complaints
 - Nail-biting, nail picking, self-scratching, self-injurious behaviors



Why does this matter?

- Anxiety affects daily living skills and interferes with adaptive functioning!

- Stress response can be adaptive, but it's not meant to be around long-term
 - Effects of chronic stress
 - Decreases in brain volume (hippocampus, etc.)
 - Short-term memory impairment (Lupien & McEwen 1997)
 - Repeated stress->cognitive dysfunction (McEwan & Sapolsky 1995)

Anxiety as a risk factor for later psychiatric illness

- High rates of psychotic features
 - Tang et al., 2013
- Baseline anxiety, low FSIQ and decline in VIQ related to psychotic disorders 4-5 years later
 - Gothelf et al., 2007 and 2013
- Anxiety is a risk factor but having anxiety in childhood does NOT mean psychotic disorders will always develop
 - Resilience and protective factors
 - Early intervention and treatment

Risk and Protective Factors

- Risk factors
 - Genetic factors
 - Exposure to stress
 - Socioeconomic status
 - Developmental delay
- Protective factors-adaptation to adversity or stress
 - Genetic factors
 - Supportive families
 - Temperament
 - Locus of control
 - Problem solving skills
 - Self regulation
 - Positive self perception

SSRIs



- Selective Serotonin Reuptake Inhibitors
- Fluoxetine (Prozac), Sertraline (Zoloft), Citalopram (Celexa)
- Fluoxetine and Sertraline: FDA approved to treat OCD and depression in children
- Mechanism:
 - Selective serotonin reuptake inhibitor
 - Targets anxiety and repetitive thoughts/ behaviors
 - Evidence: particularly effective for repetitive thoughts, well tolerated

SSRIs

- Side effects: activation, sedation, dry mouth, headaches, nausea, hyponatremia, sexual problems
 - FDA black box warning for increased suicidal thoughts in young adults and children
 - Monitoring: periodic height and weight
- No clinical trials in 22q
 - Case series in 3 adolescents with anxiety and hallucinations responded to SSRIs (Stachon and DeSouza, 2011)

Medications for anxiety may also improve executive function

- Sannar 2014 (i22q meeting abstract)
- 10 children, 4-14 years
- Anxiety decreased with pharmacological intervention
 - SSRI
 - Alpha agonists
 - Others (benzodiazepines, atypical antipsychotics, etc.)
- Improvements in adaptive and executive functioning

The home environment

- The parent-child relationship is a two-way street
- Anxious behaviors in the child affect parenting style
- Parenting style can support healthy behaviors

- An important influence on children's anxiety symptoms, especially given that cognitive behavioral therapy may be difficult to implement in children with delays

Rapee Treatment study

- Kids with increased inhibition/withdrawal are at higher risk for anxiety disorders
- Dr. Rapee looked at pre-schoolers at risk for anxiety in the general population and assessed if parent training can help reduce conversion to symptoms
- Designed a parent intervention for 6 weeks

Parents can make a difference

- Followed for 1 year in 1st study and 3 years in follow-up study with yearly anxiety assessments
- Significantly less anxiety symptoms developed in parent intervention group vs. Control group
- Reduction in symptoms was present even at 3 years
- Temperamental inhibition/withdrawal continued

What can parents do?

- Group sessions
- 90 minute sessions
 - Week 1: education about anxiety and its development
 - Weeks 2: explaining role of over-protecting in maintaining anxiety
 - Week 3-5: Cognitive restructuring and exposure hierarchies
 - Week 6: continued application as well as establishing high risk periods

Tips for healthy coping

- Have realistic expectations
- Model good coping strategies and problem solving, including taking care of yourself
- Reduce stress
- Increase your child's sense of control
- Help children identify their feelings
- Don't jump in too early (Watch, Wait, and Wonder)

Approach to treatment

- What is the target? How does the treatment work?
- How impairing is the behavior?
- What are the risks and benefits of treatment?
- How will improvement be determined?

Complementary Alternative Treatments

Melatonin

- Rationale: hormone secreted from the pineal gland to regulate circadian rhythms. May have antioxidant properties
- Evidence: several RCTs show improvements in sleep in children with intellectual disabilities and autism
- Side effects: none reported in children
 - Safe for short-term use; no data on long-term use. Should be used with bedtime routine and other behavioral interventions.
- No clinical trials in 22q

Omega 3

RESEARCH ARTICLE
Long-Chain ω-3 Fatty Acids for Indicated Prevention of Psychotic Disorders
A Randomized, Placebo-Controlled Trial
 C. Paul Ammerglan, MD; Miriam B. Schley, MD; Konstantinos Papageorgiou, MD; Charles H.engg, MD; Jay M. Cohen, PhD; Susan M. Stangor, MD; Andrew Matheson, PhD; Patrick D. McGorry, MD; Paul Cropper, E. Berger, MD

- PUFA: poly unsaturated fatty acids; cell membrane components involved in receptor binding
 - EPA and DHA (fish sources)
- Rationale: low levels of PUFA in schizophrenia
- Evidence: RCT 5% (PUFA) vs. 28% (control) progressed to psychosis in 12 months
- Side effects: GI disturbance, can impair clotting, generally safe
- No clinical trials in 22q

CAM resources

- <http://nccam.nih.gov/>
- <http://www.aap.org/healthtopics/complementarymedicine.cfm>
- www.clinicaltrials.gov



Thank you!

- To all of the families that participated in our study
- Tony Simon, Ph.D.: NIH 2R01HD42974, 1R01HD46159, 1RL1NS62412
- Elliott Beaton, Ph.D.
- CEDD-Administration on Developmental Disabilities 90DD0596
- UC Davis M.I.N.D. Institute Clinical and Translational Science Center UL1 RR024146

New study at the MIND Institute

- Parenting and adaptive functioning
 - Primary caregiver and children ages 4-11 years
 - Developmental testing
 - History and physical examination
 - Questionnaires and joint activities with child
- UC Davis CTSC K12 Scholar Project
- NIH/NCATS 8KL2TR000134-08
