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

<table>
<thead>
<tr>
<th>Children (6-12 Years)</th>
<th>Adolescents (13-17 Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>14/143 (10.0%)</td>
</tr>
<tr>
<td>ODD</td>
<td>13/143 (9.1%)</td>
</tr>
<tr>
<td>Anxious disorder</td>
<td>35/143 (24.5%)</td>
</tr>
<tr>
<td>Separation anxiety disorder</td>
<td>25/143 (17.4%)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>6/143 (4.2%)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>4/143 (2.8%)</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>1/74 (1.4%)</td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
<td>17/143 (12.2%)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>16/143 (11.2%)</td>
</tr>
<tr>
<td>Mood disorder not otherwise specified</td>
<td>6/143 (4.2%)</td>
</tr>
</tbody>
</table>

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

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
Separation anxiety in children with and without 22q

- Child self-report
- Parent report of child symptoms

Beaton et al. (ongoing study)

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 (McEwen & 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

• 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

• 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