Diagnosis and Treatment of Autism Spectrum Disorders

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Overview

- Prevalence of autism spectrum disorders (ASD)—the controversy
- Brief overview of neurobiology of ASD
- What is the appropriate work up for ASD?
- Target symptoms in ASD and mental retardation (MR)
  - ADHD
  - Stereotypies, obsessive-compulsive-like symptoms
  - Aggression and mood lability
  - Social relatedness, core symptoms of ASD?

Prevalence of ASD

- Is it really increasing?
  - Before 1990: 4.7/10,000
  - Presently: 60/10,000
- Factors related to increase
  - Addition of Asperger’s and PDD-NOS to DSM with 50-75% of new diagnoses in these categories
  - Persons with MR now more commonly diagnosed with ASD
  - Children receiving special education services for ASD went from 22,445 in 1995 to 140,254 in 2004; children getting services for MR have declined sharply
  - Appropriate abandonment of parent blaming theories have reduced stigma of diagnoses

Prevalence of ASD (Cont.)

- Even accounting for this, is there a real increase?
  - Clinical experience suggest more children presenting to the clinician with ASD-type symptoms
  - Is there any factor that might lead to a growth in prevalence of ASD?

Neurobiology of ASD

- Genetics account for 80-90% of symptom variance in ASD; the broader the ASD diagnosis, the greater the genetic effect; monozygotic twins are virtually never discordant for ASD. Multiple genes suspected- no one gene accounts for a large proportion of autism.
- No evidence at all of any relationship of ASD to immunizations
- No evidence of any toxin in the environment which has been increasing in the last 20 years- but remains controversial

If ASD is toxin related, why is the “epidemic” occurring now and not 40 years ago?
Paternal Age and ASD

- Draftees for Israeli army (universal military service)—318,506 17-year-old draftees examined
  - 110 cases of ASD identified (8.3/10,000)
  - Age of parents was available
- Offspring of men >40 years old at time of child’s birth were 5.75x more likely to have a child with ASD
- No relationship to maternal age

Reichenberg A et al. (2006), Arch Gen Psychiatry 63(9):1026-1032

Neurobiology of ASD

- Macroencephaly common in infancy and early childhood—no increase in ventricle size; brain increase is not progressive
- Magnetic resonance spectroscopy studies show high levels of phosphocreatine and phosphomonoesters in brain suggestive of high metabolism and breakdown of neural membranes
- Amygdala theory of autism—failure to recognize social stimuli—differences in face image processing in the fusiform gyrus
- Theory of mind (TOM)—“mirror” neurons that make empathy possible


Advances in genetics of ASD

- Gregory et al BMC Medicine 2009, 7:62
- 119 probands from multiplex autism families, assessed oxytocin receptor (OXTR) gene expression within the temporal cortex tissue by polymerase chain reaction (PCR).
- Epigenetic factors (gene expression) found to be important
- Oxytocin known to be important in social bonding

Neurobiology of ADHD

- Higher comorbidity of seizures than in the general population (5-49%)- wide variation probably related to sample of practitioners
- Gastrointestinal – Pica, odd food preferences, reflux, constipation- “Leaky gut” has not been proven as a major contribution as an etiology of autism
- Fragile X- 3%, Tuberous Sclerosis- 2%, maternal duplication of 15q1-13- 2%, deletions/duplications of 16p11- no specific clinical findings/treatment related to these genetic abnormalities

Screening and Diagnosis

- M-CHAT- beyond the numbers, how to discuss with parent
  - Language development
  - Social bonding/joint attention
- Key components
  - Language evaluation (Speech Therapist)
  - Psychological Evaluation (IQ, observation, structured rating scales) Ph.D. or Psychometrician vs. counselor

Screening/Detection

Office pre-Intervention

Full Diagnostic
Screening and Diagnosis

• Encourage intensive social and language interaction, even if diagnosis is not firm
• Neurological soft signs, staring, loss of consciousness, consider EEG and neurological referral
• Examine for minor physical anomalies- genetic work up
• Rapid deteriorating course- metabolic work up
• No need for MRI unless EEG or exam suggest focal lesion
• Is the Mega work up necessary?

Medical Work-Up for ASD: What Should Be Done?

• Medical work-up of 85 patients with PDD from a sample of 236 clinical patients
  – 65 (76.5%) had autism
  – 18 (21.2%) had PDD-NOS
  – 2 (2.3%) Asperger’s
• This was the subset of patient who completed all the medical work-up and structured interviews

Medical Work-Up for ASD: What Should Be Done? (Cont.)

<table>
<thead>
<tr>
<th>Etiologic Categories</th>
<th>Diagnostic Yield</th>
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<tbody>
<tr>
<td>Encephalitis (by history)</td>
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<td>Sotos syndrome</td>
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<td>Angelman</td>
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<tr>
<td>Idic (chr 15 inversion/dup)</td>
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<tr>
<td>Trisomy Chr 8</td>
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<td>Fragile X</td>
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<tr>
<td>Abnormal brain MRI</td>
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<tr>
<td>Landau-Kleffner</td>
<td>1</td>
</tr>
<tr>
<td>Deafness</td>
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</table>


Psychosocial Treatment of ASD

• Applied Behavioral Analysis (ABA)
  – Intensive reinforcement of language and social behaviors
  – Finding a certified professional: http://www.bacb.com/
  – Early Start Denver Model:

Psychopharmacology of ASD

• No specific medication treatment for ASD per se
• Treat specific target symptoms
  – Inattention, impulsivity- ADHD medications
  – Obsessive, stereotypies- SSRI’s
  – Self Injurious Behavior (SIB), grossly disorganized behavior, explosive aggression- Mood stabilizers and second generation antipsychotics
Use of Stimulants in ASD

- 72 drug-free children with PDD with moderate-to-severe hyperactivity
- 66 children who tolerated a test dose of MPH entered a 4-week crossover trial of MPH and placebo

RUPP = Research Units on Pediatric Psychopharmacology; MPH = methylphenidate hydrochloride; RUPP Autism Network (2005), Arch Gen Psychiatry 62(11):1266-1274

Use of Stimulants in ASD (Cont.)

- 35 (49%) of 72 participants were considered MPH responders, effect sizes ranging from 0.2 to 0.54, smaller than in ADHD without ASD
- Adverse events led to discontinuation of MPH in 13 (18%) of participants
- Irritability the main reason for discontinuation, but no dangerous or serious adverse events

RUPP Autism Network (2005), Arch Gen Psychiatry 62(11):1266-1274

Atomoxetine (Strattera) in ASD

- 12 children with PDD and comorbid ADHD
- 10-week open-label trial of atomoxetine (1.9 + 0.41 mg/kg/day)
- 44% reduction in ADHD-rating scale from baseline to end point (p<0.003)
- 5/12 discontinued due to adverse events—GI symptoms, irritability, sleep problems, fatigue

GI = gastrointestinal; Troost PW et al. (2006), J Child Adolesc Psychopharmacol 16(5):611-619

Atomoxetine in ASD (Cont.)

- 16 children and adolescents (mean age 7.7 ± 2.2 years) with ASD treated with open-label atomoxetine (1.2 ± 0.3 mg/kg/day) for 8 weeks
- Effect size of ADHD improvement*: 1.0-1.9
- 2/16 stopped study due to irritability
- No placebo control

*As measured by the SNAP-IV and Aberrant Behavior Checklist; Posey DJ et al. (2006), J Child Adolesc Psychopharmacol 16(5):599-610

Atomoxetine in ASD (Cont.)

- 16 children (7 autism, 1 Asperger's, 8 PDD)
- Crossover trial of 6 weeks atomoxetine (ATX), 6 weeks placebo, 1 week washout in between
- ATX superior to placebo in reducing hyperactivity symptoms, not inattention
- 9/16 responded to ATX, 4/16 to placebo


Guanfacine (Tenex) in ASD

- 25 children with ASD (mean age 9.0 ± 3.1) treated with open-label guanfacine at doses from 1-3 mg/day
- All participants had failed a trial of methylphenidate, no other medication
- 12/25 rated as “much improved” or “very much improved”

Scahill L et al. (2006), J Child Adolesc Psychopharmacol 16(5):589-598
Guanfacine in ASD (Cont.)

* $p<0.01$; †$p=0.01$; Scahill L et al. (2006), J Child Adolesc Psychopharmacol 16(5):589-598

Changes on Parent Aberrant Behavior Checklist (ABC)

- Hyperactivity
- Irritability
- Social Withdrawal
- Stereotypy
- Inapp Speech

Baseline
End point

• Adverse events N (%):
  - Sedation: 7 (28)
  - Irritability: 7 (28)—3 study termination
  - Insomnia: 6 (24)
  - Aggression: 4 (16)
  - Tiredness: 3 (12)

• No significant changes in blood pressure, pulse or EKG

Scahill L et al. (2006), J Child Adolesc Psychopharmacol 16(5):589-598

SSRIs in ASD

• Early reports (late 1970s) of elevated serotonin levels in the platelets of children with autisms
• Finding turned out not to be specific to autism (found in MR, conduct disorder)
• Similarity of many autistic symptoms to OCD
• Lead to widespread belief that SSRIs are beneficial in ASD, but clinical studies are sorely lacking

Fluvoxamine (Luvox)

• 30 adults with autism, randomized to placebo or fluvoxamine for 12 weeks
• Mean dose of fluvoxamine: 276.7 mg/day
• 8/15 on fluvoxamine improved, 0/15 on placebo
• AEs: sedation, nausea

McDougle CJ et al. (1996), Arch Gen Psychiatry 53(11):1001-1008

Fluvoxamine (Cont.)

• 34 children and adolescents with PDDs (mean age = 9.5, range 5-18 years old)
• Randomized to either fluvoxamine or placebo for 12 weeks, mean dose of fluvoxamine—107 mg/day
• Only 1/18 in fluvoxamine group responded
• Agitation, insomnia and aggression were common AEs

**Fluoxetine (Prozac)**

- 39 children (ages 5-16, mean age = 8.2) with PDD
- 20-week, placebo-controlled crossover study separated by 4-week washout
- Mean dose of fluoxetine: 9.9 mg/day (range 2.4-20 mg/day)
- Fluoxetine superior to placebo in reducing repetitive behaviors on YBOCS, no significant AEs

*YBOCS = Yale-Brown Obsessive-Compulsion Scale; Hollander E et al. (2005), Neuropsychopharmacology 30(3):582-589*

**Fluoxetine (Cont.)**

- 6/23 participants with autism treated with fluoxetine had severe AEs (hyperactivity, agitation, insomnia)\(^1\)
- Case series\(^2\)—129 young children aged 2-8 treated with fluoxetine 5-76 months, dose ranging from 4-40 mg/day; subjective clinical judgment—69% had a “positive response rate”

\(^1\)Cook EH et al. (1992), J Am Acad Child Adolesc Psychiatry 31:739-745; \(^2\)DeLong GR et al. (2002), Dev Med Child Neurol 44(10):652-659

**Citalopram and ASD**

- King et al. Arch Gen Psychiatry 2009 66:583
- 149 children aged 5-17 (mean age 9) with ASD
- Randomized to placebo or citalopram for 12 weeks
- Mean dose of citalopram 16.5 mg/day
- Multiple outcome measures
- Multi-cent study

**No efficacy of citalopram**

**Risperidone in Adults With MR**

- 33 institutionalized retarded adults, only 3 diagnosed with psychosis NOS
- Risperidone dose = 1-8 mg/day
- After 6 months, 85% of patients improved
- Wages earned by patients in B-mod program increased 37%

*Lott RS et al. (1996), Psychopharmacol Bull 32(4):721-729*
RUPP Risperidone Study

- 101 children (mean age 8.8 ± 2.7 years) randomly assigned to receive risperidone (N=49) or placebo (N=52) for 8 weeks
- Risperidone dose: 0.5-3.5 mg/day


RUPP Risperidone: Irritability

Mean Irritability Score

Placebo
Risperidone

p<0.001; Irritability on Aberrant Behavior Checklist; RUPP Autism Network; McCracken JT et al. (2002), N Engl J Med 347(5):314-321

RUPP Risperidone: CGI-I

Respondees: 69% Risperidone
12% Placebo

CGI-I = Cognitive Global Impressions - Improvement Scale

RUPP Risperidone: Safety

- Significantly higher weight gain (mean 2.7 kg) in risperidone vs. placebo group (mean 0.8 kg)
- Increased appetite
- Drowsiness (49% vs. 12% on placebo)
- No difference in dyskinesia between risperidone and placebo


RUPP Risperidone: Discontinuation Study

- 63 children completed 4 months of treatment with risperidone after 8-week controlled trial
- 38 entered an 8-week, double-blind discontinuation phase, randomized to continue risperidone or switch to placebo

Risperidone in ASD

- 40 children with autism, ages 2-9
- Randomized to placebo or risperidone for 6 months
- 17/19 children in risperidone group showed improvement by CGAS vs. 0/20 in placebo group

Note: Study ended as NIMH Data and Safety Monitoring Board (DSMB) felt further exposure to placebo not warranted

CGAS = Children's Global Assessment Scale; Nagaraj R et al. (2006), J Child Neurol 21(6):450-455

Risperidone in Preschoolers: Safety Data

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<thead>
<tr>
<th></th>
<th>Risperidone</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Weight change (kg)</td>
<td>2.96*</td>
<td>0.61</td>
</tr>
<tr>
<td>Leptin change (mg/L)</td>
<td>0.66*</td>
<td>-0.35</td>
</tr>
<tr>
<td>Prolactin change (ng/ml)</td>
<td>33.40*</td>
<td>11.10</td>
</tr>
</tbody>
</table>

*p<0.05; Luby J et al. (2006), J Child Adolesc Psychopharmacol 16(5):575-587

Aripiprazole in ASD

- 8-week, double-blind, randomized, placebo-controlled, parallel-group study was conducted of children and adolescents (aged 6–17 years) with autistic disorder
- 98 patients were randomly assigned (1:1) to flexibly dosed aripiprazole (target dosage: 5, 10, or 15 mg/day) or placebo
- Discontinuation rates as a result of adverse events (AEs) were 10.6% for aripiprazole and 5.9% for placebo. Extrapyramidal symptom-related AE rates were 14.9% for aripiprazole and 8.0% for placebo. No serious AEs were reported. Mean weight gain was 2.0 kg on aripiprazole and 0.8 kg on placebo at week 8.
Aripiprazole in ASD

Algorithm for Treatment of ASD

- Define problematic domains
  - Attention/impulse control/hyperactivity (ADHD)
  - Repetitive behaviors, obsessive stereotypies
  - Severe problems
    - SIB
    - Explosive aggression
    - Mood lability
- Broad social interaction/language problems should be the focus of intensive psychosocial interaction