A Review of the State of the Science in Autism Spectrum Disorder: Lights on the Horizon:

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Learning Objectives

Review contemporary definition and epidemiology of Autism Spectrum Disorder (ASD).

Provide an overview of new developments in the field, including

- Causes of ASD
- Genetic Diagnosis
- Behavioral treatments and improved outcomes
- Medical treatment of core symptoms of ASD

Describe implications of scientific advances for a new vision of treatment for children with ASD
DSM-5 and Revised Diagnostic Criteria for Autism Spectrum Disorders

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
   1. Deficits in social-emotional reciprocity
   2. Deficits in nonverbal communicative behaviors used for social interaction
   3. Deficits in developing, maintaining and understanding relationships

B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following, currently or by history:
   1. Stereotyped or repetitive motor movements, use of objects or speech
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior
   3. Highly restricted, fixated interests that are abnormal in intensity or focus
   4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment

C. Symptoms must be present in the early developmental period.

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability or global developmental delay.

• 227 subjects seen for multi-disciplinary assessment with DSM-IV-TR and DSM-5 checklists; 83.7 % were male; median 3.95 years

• DSM-5 was psychometrically superior to the DSM-IV-TR model

• Children with DSM-IV “autistic disorder” were more likely to meet DSM 5 social communication and repetitive behaviors criteria than those with “PDD-NOS”

• 156 subjects who met DSM-IV-TR criteria for an autism spectrum disorder, 23% ($N = 36$) did not meet DSM-5 ASD criteria

Epidemiology

• Widely divergent prevalence figures, ranging from 0.7 to 15.5 per 10,000 persons

• Centers for Disease Control Autism and Developmental Disorders Monitoring most recent estimate is 1 of every 68 8-year-olds—or is it 1 in 45???

• Concerns about apparent increased frequency of occurrence in past 10 to 15 years
  • if real, could this be due to “environmental factors”
  • if not, could it be due to increased use of more well defined diagnostic criteria
Table 2. Age- and Sex-Adjusted Incidence of Research-Identified Autism

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Incident Cases</th>
<th>Incidence Rate Per 100 000 People (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976-1979</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1980-1983</td>
<td>7</td>
<td>5.5 (1.4-9.5)</td>
</tr>
<tr>
<td>1984-1987</td>
<td>11</td>
<td>7.9 (3.2-12.6)</td>
</tr>
<tr>
<td>1988-1991</td>
<td>18</td>
<td>11.8 (6.3-17.3)</td>
</tr>
<tr>
<td>1992-1994</td>
<td>34</td>
<td>29.4 (19.4-39.3)</td>
</tr>
<tr>
<td>1995-1997</td>
<td>54</td>
<td>44.9 (32.9-56.9)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
*Age- and sex-adjusted to the structure of the US white population 21 years or younger in 2000.

Overall age- and sex-adjusted incidence per 100,000 children by period of research-identified autism (A) and all other clinical diagnoses of developmental, neurologic, and psychiatric disorders (B) among residents of Olmsted County, Minnesota, between 1976 and 1997.
Conclusions

• Possible explanations for the apparent increase in Autism incidence
  • Publication of DSM-III-R, DSM-IV
  • Effects of passage of special education laws
  • Increased awareness of autism
  • Our findings **DO NOT** suggest that immunization policies have caused the incidence of autism to increase
  • True increase in the incidence of autism?

• Study recently published in England: Epidemiology of Autism in Adults
  • prevalence of 9.8 cases of autism spectrum disorder per 1,000 population—**SAME AS HIGHEST CHILDHOOD PREVALENCE ESTIMATE**
  • “…our findings suggest that prevalence is neither rising nor falling significantly.”
Etiology: Genetics

• As recently as 1976, genetics not believed to play a role in ASD

• Series of twin studies reversed this belief
  • High rate of concordance in monozygotic twins, low or rare in dizygotic twins

• Familial incidence (sibling risk - 8% - other figures as well) – High risk sib studies 20%
Progress

• We are now where oncology was 30 years ago
• Our Problem: We had no way to get at the brain except observation BUT NOW:
  • Human genome project and genomics
  • Knock out animal models of single gene disorders for treatment trials
  • Progress in neuroscience
  • New cognitive neuroscience tools including
    • New functional imaging techniques
    • ERP ("Evoked Response Potential")
    • MEG ("Magnetoencephalography")
• Potential of stem cell to neuron – “Personalized Medicine”
Known causes of autism are individually rare—Autism or the “Autisms”

Clinically recognizable syndromes:
- Fragile X (FMR1)
- Tuberous Sclerosis (TSC1/TSC2)
- Angelman (UBE3A)
- Smith Magenis Syndrome (Del 17)
- Rett’s Syndrome (MeCP2)
- Down Syndrome
- William’s Syndrome (Del 7)
- Duchenne Muscular Dystrophy

Recurrent chromosomal abnormalities:
- 16p11.2
- 15q11-13,
- 22q11
Known causes of autism are individually rare

- **Private, de novo CNVs**: 8%
- **Syndromic + Other monogenic**: ~4%
- **Chromosomal abnormalities**: ~3%
- **Unknown**: 85%

Other monogenic disorders:
- Neurexin 1, NLGN3/4, SHANK3, CNTNAP2, ...

Private *de novo* CNVs

Unknown – 85%
Change in Clinical Practice: Genetic Evaluation of Children with Autism

- Molecular DNA test for Fragile X syndrome
- Chromosomal microarray
- Others as indicated by clinical presentation (e.g., High resolution karyotyping)
- Routine part of care
Genomic Screening for ASD in Primary Care: Current Clinical Study
Contemporary Treatment for Autism Spectrum Disorders

- Behavioral (Applied Behavior Analysis)
- Educational
- Pharmacologic
Intensive Behavioral Treatment for Autism: Applied Behavior Analysis (ABA)

• Based on principles of operant conditioning
• Teaches specific social, communicative and behavioral skills to children with ASDs by explicit reinforcement of these behaviors
• Requires careful data collection to demonstrate efficacy of treatment for the individual child; data used to assess progress toward specific objectives
• Work of Lovaas et al (1987) suggested 50% of young children with autism had “normal” long-term development after 2 years of intensive ABA (40 hours per week)
• Subsequent, randomized studies show significant improvement, but NOT as often or to the degree suggested by Lovaas’ original work
• Best prognosis is for less severely affected children
Outcomes of Intensive Intervention Before 3 years of Age

• Fein et al– 20% in normal classrooms – no special education

• CHB phenotype/genotype study – 20% no longer meet criteria for ASD 2 years after original clinical diagnosis

• Dawson et al, Pediatrics -2010-Early Start Denver Model – RCT – N=48; IQ (18 vs. 7), Adaptive function, change in Dx from Autism to PDD

Project TEACCH (*Treatment and Education of Autistic and Related Communication Handicapped Children*)

- The TEACCH mission is:
  - To enable individuals with autism to function as meaningfully and as independently as possible in the community

- General principle is to take advantage of strengths in visually based cognitive skills

- Visual schedules

- “Work stations”

- Picture Exchange Communication System (PECS)

- Structured physical environment
Common Sense Treatment

• Behavioral and educational approaches both have solid theoretical foundations
• Neither is likely to be the “answer” for Autism intervention
• The level of intensity of service does seem to be important
• Empirical evidence indicates ABA should be viewed as the optimal treatment approach
Medical Treatment of Behavior Problems in Children with Autism

• No medication improves “core symptoms” of autism…**YET**

• Other behaviors are common and have adverse impact
  • Hyperactivity, irritability, stereotypy

• Randomized trials demonstrate effectiveness atypical antipsychotic medication (risperidone, now FDA approved for this indication)

• Stimulant medications (e.g. methylphenidate, mixed amphetamine salts) improve hyperactive, impulsive, inattentive behaviors

• Mayo Epidemiology of Autism Study
  • 124 subjects, 52.4% treated with stimulant medications
  • 398 distinct episodes of treatment
  • 69.4% of treatment episodes associated with improvement in target behaviors
Known autism genes often relate to the synapse
A common signaling pathway
Potential for Future Medical Treatment of Core Symptoms of Autism: Animal Studies of Fragile X Syndrome

- Fmr1 knockout mice manifest phenotypic characteristics of human Fragile X Syndrome
  - Increased density of dendritic spines on cortical pyramidal neurons
  - Audiogenic seizures
  - Accelerated body growth
  - Macroorchidism
- Double knockout mice (Fmr1 AND 50% reduction in mGluR5) restored wild-type phenotype (i.e., eliminated characteristics of Fragile X syndrome)
- Multiple compounds block the mGluR5 receptor, reversing Fragile X symptoms in mice—HUMAN TRIALS UNDERWAY
mGluR5 genetic rescue of dendritic spine morphology

Dolen et al., 2007
ASD/FXS pathophysiology: Synaptic excitation: inhibition imbalance

- Normal experience-dependent learning
- Excessive glutamate release and excitation
- Insufficient GABA inhibition
- Increased seizure susceptibility
- Sensory hyperarousal
- Emotional dysregulation
- Altered synaptic plasticity

- Decreased excitation by reducing presynaptic glutamate release
- Normalized post-synaptic signaling processing
Implications of Genetic Advances: Medical Treatment for ASD

• Multiple studies underway

• Medications that impact the neuronal synapse, regulate protein synthesis

• Early, promising findings
  • Social functioning
Cognitive Neuroscience and Early Identification of ASD

Collecting EEG/ERP (Evoked Response Potential) Data
Early Identification of ASD in High Risk Infants

• Early high risk infant sib consortium across US, Canada and Europe (started earlier)
• Being seen starting at 3-6 months + every 3 to 6 months
• Applying different technologies at 6 months:
  • Nelson, et al – has identified an EEG signature that distinguishes infants at high risk for developing autism and who are subsequently diagnosed with autism from those at equal risk but who do not develop the disorder
  • British Autism Study of Infant Siblings (BASIS) - Difference in ERP’s – faces looking at or looking away
  • Piven, et al – DTI’s different in children with ASD
Autism Spectrum Disorders: A New Treatment Vision

- **Dx at Birth**
- **Age**
- **Disease Severity**

- **Early Therapy**
  - Targeted Therapy
    - Based On Disease Subcategory
    - New Insights Into Use of Existing medications

- **Current Treatment**
  - Aggressive Behavioral
  - Drugs for Symptoms

- **New Therapeutics**
  - Potential Early Use of Existing meds
  - New Autism Therapy
  - Intensive Early Behavioral Therapy

- **Symptomatic**

- **No Treatment**

- **Dx at Age 3**

- **Age**
Selected References


• Clinical Practice Guideline, Report of the Recommendations, Autism/Pervasive Developmental Disorders, NY State Department of Health Early Intervention Program,


Websites

• www.firstsigns.org (has links to CHAT and M-CHAT)
• www.abainternational.org
• www.lovaas.com (Applied Behavior Analysis)
• www.asatonline.org (Association for Science in Autism Treatment)
• www.teacch.com (Project TEACCH homepage)