NEURODIVERSITY IN AUTISM SPECTRUM DISORDERS: Updates on Neurobiology and Clinical Diagnosis

Ermenilda L. Avendano, M.D.
Child Neurologist
Neurodevelopmental Pediatrician

9th PSDBP Biennial Convention
Avendano MD
Lifelong behaviorally defined, neurologically based developmental disorder of brain functioning

It is a heterogeneous group characterized by a clinical dyad of impaired social-communication function and the presence of restricted, repetitive patterns of behaviors and interests.

There exists a tremendous phenotypic heterogeneity in adaptive function, cognitive and language abilities and neurological morbidities.
- Definition
- Diagnostic Criteria
- Neurobiology
- Clinical Manifestations
- Outcomes
PERVASIVE DEVELOPMENTAL DISORDERS

AUTISM SPECTRUM DISORDERS

- Autistic Disorder
- PDD-NOS
- Asperger’s Syndrome

Rett’s Syndrome

Childhood Disintegrative Disorder

DSM 4 TR

9th PSDBP Biennial Convention
Ermenilda Avendano MD
AUTISM SPECTRUM DISORDER

DSM-5
May 2013
# AUTISM SPECTRUM DISORDER 299.00(F84.0)

**A. PERSISTENT DEFICITS IN SOCIAL COMMUNICATIONS AND SOCIAL INTERACTIONS ACROSS MULTIPLE CONTEXTS AS MANIFESTED BY THE FOLLOWING, CURRENTLY OR BY HISTORY (must meet all)**

1. **Deficits in social-emotional reciprocity**  
   Abnormal social approach and failure of normal back-and-forth conversations  
   Reduced sharing of interests, emotions or affect,  
   Failure to initiate or respond to social interactions

2. **Deficits in non-verbal communicative behaviors** used for social interaction,  
   Poorly integrated verbal & nonverbal communications  
   Abnormalities in eye contact & body language  
   Deficits in understanding & use of gestures  
   Lack of facial expressions & non-verbal communications

3. **Deficits in developing, maintaining and understanding relationships**  
   Difficulties adjusting behavior to suit various social contexts  
   Difficulties in sharing imaginative play or in making friends  
   Absence of interest in peers

B. RESTRICTED, REPETITIVE PATTERNS OF BEHAVIOR, INTEREST OR ACTIVITIES, AS MANIFESTED BY **AT LEAST 2** OF THE FOLLOWING, currently or by history

1. **Stereotyped or repetitive motor movements, use of objects or speech**
   - Simple motor stereotypies, lining up toys or flipping objects
   - Use of objects
   - Echolalia, idiosyncratic phrases

2. **Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior**
   - Extreme distress at small changes, difficulty with transitions, rigid thinking pattern, greeting rituals
   - Need to take same route or eat same food every day

3. **Highly restricted, fixated interests that are abnormal in intensity or focus**
   - Strong attachment to or preoccupation with unusual objects
   - Excessively circumscribed or perseverative interests

4. **Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of environment**
   - Apparent indifference to pain/temperature
   - Adverse response to sound or textures
   - Excessive smelling, touching, visual fascination to lights or movement

C. Symptoms must be present in the early developmental period (but may not become full manifest until social demands exceed limited capacities or may be masked by learned strategies in later life).

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 (ID) or global developmental delay. ID and autism may co-occur; to make comorbid diagnosis of ASD and ID, social communication should be below the expected for general developmental level.
**SPECIFY IF:**

<table>
<thead>
<tr>
<th>With or without accompanying intellectual impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>With or without accompanying language impairment</td>
</tr>
<tr>
<td>Associated with a known medical or genetic condition or environmental factor</td>
</tr>
<tr>
<td>Associated with another neurodevelopmental, mental or behavioral disorder</td>
</tr>
<tr>
<td>With catatonia</td>
</tr>
</tbody>
</table>
# SEVERITY LEVELS FOR AUTISM SPECTRUM DISORDER

**DSM-5**

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>Social Communication</th>
<th>Restricted Interests, Repetitive Behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEVEL 3</strong></td>
<td>Severe impairments in communication</td>
<td>Marked interference with functioning at all spheres.</td>
</tr>
<tr>
<td><strong>Requiring very</strong></td>
<td>Minimal social communication</td>
<td>Great distress changing focus</td>
</tr>
<tr>
<td><strong>substantial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>support</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LEVEL 2</strong></td>
<td>Marked deficits in communication</td>
<td>Appears frequently enough to be obvious to casual observer</td>
</tr>
<tr>
<td><strong>Requiring</strong></td>
<td>Reduced social interaction</td>
<td>Distress changing focus</td>
</tr>
<tr>
<td><strong>substantial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>support</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LEVEL 1</strong></td>
<td>Without supports, noticeable impairments</td>
<td>Significant interference in at least one context</td>
</tr>
<tr>
<td><strong>Requiring</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>support</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Complete Diagnosis
Autism Spectrum Disorder

8 year old female
Congenital rubella syndrome
Sensorineural hearing loss, AU
Epilepsy

Met ASD diagnostic criteria
Non-verbal
Approaches only for needs
Distressed with changes
Self injurious behaviors
Maximally assisted in ADLs

Developmental abilities – from 8 months to 3 years

Specifiers:
• With language impairment
• With intellectual impairment
• With congenital rubella syndrome
• With epilepsy
• With hearing impairment, AU

Severity Level:
Level 3 – requiring very substantial support in social communication
Level 3 – requiring very substantial support in restricted and repetitive patterns of behaviors, interest and activities
When Does Autism Start?

When Are Symptoms Recognized?

Symptoms typically observed by **12-24 mths**
(15-18 mths)

May not become fully manifest until **social demands exceed limited capacities**, or may be **masked by learned strategies** in later life.

May be seen
**< 12 months**
Red Flags In Young Children That May Indicate The Presence of ASD

Parents and caregivers should be alert to the following red signs:

- No **babbling** by 12 months
- No **pointing or gesturing** by 12 months
- No **single words** by 16 months
- No **2-word phrases** by 24 months

- **Loss of previously acquired skills, especially language**

Autism New Jersey. Autism: Start Here, 2nd ed 2014
Red Flags In Young Children That May Indicate The Presence of ASD

- Lack of **joint attention** (child does not draw other’s attention to objects in environment)
- Does not **respond to name**
- Lack of **pretend, imitative and functional play** appropriate for developmental age
- Failure to develop **peer relationships** appropriate to developmental age
- Does not **imitate others’ behaviors**
- Rigid in routines or has very difficult **transitions**
- Engages in repetitive or stereotypical **behavior**
- Unusual **response to sensory stimuli**
Genetic Influences

Environmental Influences

Epigenetics

Neurobiology

Structure
Connection
Function

BEHAVIORAL MANIFESTATIONS
Can a larger than normal head size be a biological signature for ASD?

- Previous studies have implicated presence of macrocephaly in a greater number of ASD children

- Longitudinal studies showed abnormal rapid increase in head circumference from 6-14 mths.

- Other studies: Larger heads than unaffected siblings but difference is small (2 mm on average). Inconsistent support for early brain overgrowth in ASD. 

Raznahan A et al. Biol Psychiatry 2013 Oct 15
• Volume abnormalities in both grey and white matter
• Most replicated: early brain overgrowth esp. in frontal region (first 2-3 years), temporal, limbic regions
• Precocious enlargement of the amygdala
• Cerebellar hypoplasia

Anagnostou E and Taylor, M. Review of Neuroimaging in ASD: What Have We Learned and Where We Go From here, Mol Autism: 2011, 2:4
To see how people with autism respond to cognitive tasks: Social intelligence, cognitive control and communication (primary cognitive processes associated with core deficits of ASD)

Decreased cortical specialization: Mild shifting of cortical location in response to a variety of tasks

Anagnostou E and Taylor, M. Review of Neuroimaging in ASD: What Have We Learned and Where We Go From here, Mol Autism: 2011, 2:4
The Secret In Their Eyes

Hypoactivity in the fusiform gyrus during face recognition tasks

- Consistent fMRI finding confirming clinical impression that deficits in facial recognition seen in ASD

- Demonstrated associated deficits in related areas of the “social brain”, such as amygdala (emotion and arousal) and integration of emotional data

- Eye tracing techniques revealed they pay less attention to faces and more attention to inanimate details in the background
Environmental Influences

- “Second hit” or “trigger” phenomenon in susceptible individuals
- Increase chances for developing ASD when combined with genetic influences
- By itself unlikely to cause ASD
- May involve epigenetics
# Environmental Influences Cited

<table>
<thead>
<tr>
<th>PRIOR TO OR DURING BIRTH</th>
<th>PERI- AND POST-NATAL FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced parental age</td>
<td>Air and water pollution</td>
</tr>
<tr>
<td>Maternal nutrition deficiencies</td>
<td>Persistent organic pollutants (PCB)</td>
</tr>
<tr>
<td>Assisted reproduction</td>
<td>Pesticides- organophosphate</td>
</tr>
<tr>
<td>Prenatal exposure to pollution</td>
<td>Non-persistent organic pollutants (phthalates, BPA, PVC floorings)</td>
</tr>
<tr>
<td>Maternal obesity or diabetes</td>
<td>Viruses</td>
</tr>
<tr>
<td>Extreme prematurity</td>
<td>Food</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>Vaccine ingredients</td>
</tr>
<tr>
<td>Birth difficulty leading to periods of prenatal O2 deprivation</td>
<td>** ?? TV, gadgets, radiation**</td>
</tr>
<tr>
<td>Prenatal exposure to pesticides</td>
<td></td>
</tr>
</tbody>
</table>

Environmental Influences Cited

9th PSDBP Biennial Convention
Ermenilda Avendano MD

5 Sept 2017

ELAvendano
Is there a link between Autism and Vaccines?
Autism Occurrence by MMR Vaccine Status Among US Children with Older Siblings With and Without Autism

Anjali Jain, MD; Jaclyn Marshall, MS; Ami Buikema, MPH; Tim Bancroft, PhD; Jonathan P. Kelly, MPP; Craig J. Newschaffer, PhD

JAMA. 2015;313(15):1534-1540

**IMPORTANCE** Despite research showing no link between the measles-mumps-rubella (MMR) vaccine and autism spectrum disorders (ASD), beliefs that the vaccine causes autism persist, leading to lower vaccination levels. Parents who already have a child with ASD may be especially wary of vaccinations.

**OBJECTIVE** To report ASD occurrence by MMR vaccine status in a large sample of US children who have older siblings with and without ASD.

Subjects: 95,727 children with older siblings

**CONCLUSIONS AND RELEVANCE** In this large sample of privately insured children with older siblings, receipt of the MMR vaccine was not associated with increased risk of ASD, regardless of whether older siblings had ASD. These findings indicate no harmful association between MMR vaccine receipt and ASD even among children already at higher risk for ASD.
NEUROBIOLOGY OF AUTISM

Fragile Genes
Multiple genes
None exclusive to ASD

Cell-to-cell transmission affected

Abnormal brain growth
Gray and white matter differences

Excessive intrahemispheric
Deficient interhemispheric

9th PSDBP Biennial Convention
Ermenilda Avendano MD
There is no visual phenotype. There is no biological marker for diagnosis. We see its etiologic complexity.

Behaviors emerge from a complex interplay between pre-existing neurodevelopmental vulnerabilities and the child’s environment.

Varied clinical manifestations of social communication issues and restricted and repetitive patterns of interest and activities, varied cognitive abilities and co-morbidities.
ASSOCIATED CONDITIONS

- Cognitive deficits
- Epilepsy
- Sensorimotor symptoms
- Feeding difficulties
- Sleep problems
- ADHD
- Mood disorders
- Anxiety disorders
AUTISM SPECTRUM DISORDER

Adapted from Understanding the Spectrum
The-art-of-autism.com
“If you’ve met ONE individual with autism, you’ve met ONE individual with autism.”

Stephen M. Shore
Pathways and Trajectories

- Autism severity does not track with ability to function in daily life
- What is the better desired outcome:
  - Reduction in autism or Improvement in symptoms
  - Improvement in adaptive functioning

- What will my child be able to do – or not do when he gets older?
- How many years of therapy will he need to be okay?
- Will my child stay low functioning forever?

Szatmari et al. Developmental Trajectories of Symptom Severity and Adaptive Functioning. JAMA Psych 2015
Georgiades et al. Tracing autism’s trajectories could help explain diversity. Spectrum. May 2017
Instead of focusing exclusively on the impairments experienced by individuals with autism spectrum disorder, concentrate on their cognitive diversity and strengths.

This approach will not only improve our understanding of the condition but will also promote better social engagement and fulfillment for people with ASD and other cognitive differences.