Co-occurring medical conditions impacting health and behavior in Autism Spectrum Disorders

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Is autism a biological or behavioral disorder?
Definition of Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a biologically based neurodevelopmental disorder.

- **Biological** = based in structural or functional processes of the human body*
- **Neuro** = brain and nervous system
- **Developmental** = affecting normal growth and development
- **Disorder** = life long
Definition/Diagnostic Criteria

- The criteria established that define what characterizes autism = outward expression, or symptom, of a brain based disorder
Diagnostic Criteria

- **DSM-5** — The DSM-5 diagnosis of ASD is characterized by:

- Persistent deficits in social communication and interaction (e.g., deficits in social reciprocity; nonverbal communicative behaviors; and skills in developing, maintaining, and understanding relationships), and

- Restricted, repetitive patterns of behavior, interests, or activities
Epidemiology

- 1 in 68
- 4:1 boys to girls
- Advanced parental age (both paternal and maternal) has been associated with an increased risk of having a child with ASD
Epidemiology

increased prevalence

Epidemiologic studies of autism say “no” and revealed:

• changes in case definition
• increased awareness
• earlier detection, availability of more specialized developmental services
• diagnostic substitution
Genetics - what is the cause of ASD?

***Not yet known or well understood***

Consensus in the scientific community

Genetic cause $\rightarrow$ alters brain development $\rightarrow$ abnormal social, communication development and restricted interests/repetitive behavior
Genetics

Among the families in which the older child had ASD, the risk of recurrence varied as follows according to the sex of the siblings:

- Younger brothers of girls with ASD – 17 percent
- Younger brothers of boys with ASD – 13 percent
- Younger sisters of girls with ASD – 8 percent
- Younger sisters of boys with ASD – 4 percent
Cause(s) of Autism - unknown

- In-utero exposure (maternal medications, illness)
- In-utero dysgeneis (malformation)
- Abnormal connectivity/pruning
- Genetics(specific genetic syndromes associated with ASD/runs in families)
- Environmental Toxins( ie Air Pollution)
Neurobiologic factors

Brain abnormalities play an important role (as seen via brain imaging and autopsy). These abnormalities include, as compared to those without ASD:

Differences in:

grey and white matter volumes
Sulcal and gyral anatomy
Brain chemical concentrations
Neural networks
Cortical structure and organization
Brain lateralization
Cognitive processing
Autism and the Brain

Autism and the Brain

autism awareness autism autistic brain
Neurobiology of sensory issues

- Hypersensitivity in brain areas responsible for processing of sensory information and emotions
Neuro-biological factors

support for brain abnormalities: observations

- Accelerated head growth during infancy and increased overall brain size

- Functional MRI-different patterns of connectivity, cognitive strategies, and brain areas to process information during tasks requiring social attribution or response to verbal or auditory stimuli

- PET scans-children with ASD have global and functional abnormalities of serotonin synthesis
Autism and the Brain
Neuroplasticity

- Neuron regeneration
- Reorganization
- Pruning
- Most active period 1st 2 years of life
Increased neural activity in autism

Typically developing children

Children with autism
Associated Medical Conditions (Comorbidities)

- Fewer than 10 to 25 percent of cases of ASD are associated with a medical condition or known syndrome.

- Associated medical conditions are more common in patients with comorbid global developmental delay or intellectual disability.
Genetic disorders associated with ASD

The most common associated genetic disorders include:

- **Tuberous Sclerosis Complex (TSC)** –
  ~17 to 60 percent of patients with TSC also have ASD
  ~only 0.4 to 4 percent of patients with ASD have TSC
  ~Patients with comorbid tuberous sclerosis complex and ASD often have epilepsy

- **Fragile X** –
  ~As many as 30 to 50 percent of patients with fragile X syndrome have features of ASD (e.g., deficits in social interaction and communication, repetitive and stereotyped behaviors)
Fragile X

Typical facial features in a patient with fragile X syndrome

A four-year-old boy with fragile X syndrome displays some of the typical facial features of the disorder including:
- A long and narrow face with prominent forehead and chin (prognathism)
- Large ears
- Midface hypoplasia with sunken eyes
- Strabismus
Fragile X syndrome

- Inactivation of FMR-1 gene at X q27.3 due to CGG base repeats, methylation
- X-linked Recessive.
  - 1:1000 male births
  - 1:3000 female
- Accounts for 10-12% of ID in males
  - #1 heritable cause
  - #2 chromosomal cause
Fragile X Syndrome

Physical Features

- Large head/ears
- Long narrow face
- Macroorchism (enlarged testes)
- Velvety skin
- Connective tissue abnormality
  - Hyperextension, aortic root enlargement
Fragile X Syndrome

Cognitive/Behavioral Features

- Hyperactivity, inattention
- ASD
  - Stereotypes
  - Speech and language delays
  - Learning disabilities
  - Gaze aversion, social avoidance, shyness
- Verbal IQ > Performance IQ
- ID
  - Mild – in affected females
  - Moderate – severe in males
Fragile X Syndrome

OTHER ISSUES
• Communication skills
• ADHD
• Stereotypes
• Anxiety symptoms
• Social shyness
• All of the above can lead to irritability and aggression
Tuberous Sclerosis complex

- 17-60% of patients with TS also have ASD
- Only 0.4-4% of patients with ASD have TS
- Patients with comorbid TS complex and ASD also have epilepsy
TABLE 4.
Surveillance and Follow-Up Testing After a Tuberous Sclerosis Diagnosis

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin, eyes</td>
<td>Annual clinical examination</td>
</tr>
<tr>
<td>Teeth</td>
<td>BI-annual clinical examination</td>
</tr>
<tr>
<td>Brain</td>
<td>Brain MRI every 1-3 years until age 25 years, EEG based on clinical need, TAND screen annually</td>
</tr>
<tr>
<td>Heart</td>
<td>ECHO every 1-3 years until regression of rhabdomyoma, EKG every 3-5 years</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Annual blood pressure measurement, annual GFR measurement, abdominal MRI every 1-3 years</td>
</tr>
<tr>
<td>Lungs</td>
<td>PFT annually, HRCT every 5-10 years or every 2-3 years*</td>
</tr>
</tbody>
</table>

Abbreviations: EEG, electroencephalogram; ECHO, echocardiogram; EKG, electrocardiogram; GFR, glomerular filtration rate; HRCT, high-resolution chest computed tomography; MRI, magnetic resonance imaging; TAND, TSC (tuberous sclerosis complex) associated neuropsychiatric disorder; PFT, pulmonary function testing.

*If evidence of lymphangiomyomatosis. Adapted from Krueger and Northrup.
The answer to your dreams:
Rett syndrome

- Progressive X-linked encephalopathy
- Affecting 1:10-15,000 females.
- MECP2 gene
RETT Syndrome

Rett’s syndrome

- Stage I-early-onset-6-18 months of age
  - Often overlooked because of vague/subtle symptoms
  - Diminished eye contact + reduced interest in toys
- Stage II-rapid destructive stage 1-4 years
  - Loss of purposeful hand movements + language
- Stage III-Plateau phase-2-10 years
  - Apraxia + seizures prominent
- Stage IV-late motor deterioration stage-years or decades
  - Reduce motility, scoliosis, muscle weakness, rigidity, spasticity, inability to walk.
Rett syndrome

- Early development is normal.

- At 5-48 months of age, deceleration of head growth and loss of previously acquired purposeful hand movements

- Stereotyped midline hand movements (wringing, washing, clapping, mouthing)

- Gait and truncal apraxia/ataxia follow
  - Wide-based gait
Rett syndrome

- Apraxia = inability to perform motor functions
- EEG abnormalities/seizures
- Breath holding/hyperventilation common
- Severely impaired expressive/receptive language
- Autistic features
- Males usually expire early in life
- Women may live into their 40s + 50s with the disorder
Angelman Syndrome

- Facial features
  - Large mandible, open mouth expression
- Hypotonia, ataxia, jerky arm movements
  - Puppet like
- Seizures
- Language severely impaired or absent
- Frequent smiling
  - “Happy puppet”
- Outbursts of laughter
- Autistic features and aggression may be seen.
- Repetitive/stereotyped behavior
Epilepsy in ASD

- 20 % in individuals with ASD
- May be later onset
- Be on the look-out.
Epilepsy in ASD

- More common in individuals with ASD and intellectual disability (ID) as compared to those with ASD alone
- 21.5%:8% (which is higher than general population)
- Male:Female 2:1 compared to 3.5:1 is those w/o epilepsy
- ID greatly increases the risk of epilepsy
Epilepsy and ASD

Does Epilepsy cause ASD???

- West syndrome (infantile spasm)-of associated with TSC
- Landau-Kleffner-abnormal EEG with language regression
Electroencephalogram (EEG)

- Several types of seizures which have different EEG wave patterns and clinical manifestations (generalized, complex, partial complex, absence)
- Required routinely in ASD-controversy
- 24 hour EEG
- Treating the EEG
- Treatment with anticonvulsant medications
GI Symptoms

- Children—more GI symptoms compared to controls
- 5X increase in feeding problems
- Prefer starches, snack foods, processed foods
- Controversy—cause of ASD vs result of ASD?

~abnormal immune function or elevated intestinal permeability
~Gluten sensitivity
~Lactose Intolerance
Gastrointestinal Issues in ASD

- Leaky gut
- GE reflux
- Special diets-GFCF
- Constipation
- Encopresis
GI Issues

- constipation
- encopresis
- Loose stools
- Restrictive food intake-nutrition deficiency/FTT
Inadequate Nutrition

- common
- low calcium intake—needed for strong bones
- low protein intake
- restrictive eating—too much milk → anemia
Constipation
Pathogenesis of functional constipation

Discomfort

Withholding behavior

Retained Stool

Overflow incontinence

Dietary Changes
  e.g. switch to solid foods

Psychosocial stressors
  e.g. toilet training, start of school

Behavioral Adaptations
  e.g. Pain, anxiety, punishment

Incomplete rectal emptying

↓ Sensitivity and motility

Usually no physiological differences
ENCOPRESIS
PATIENT TRAINING DIAGRAM

NORMAL INTESTINE (COLON)
- Warning Nerves
- Body Waste
- Strong, Thick Muscle

STRETCHED INTESTINE (MEGACOLON)
- Body Waste Hard and Large (Like Rocks)
- Muscle That's Thin, Weak and Stretched
- Nerve Out Nerves That Don't Work
- Space Between ROCKS

STRETCHED INTESTINE KEPT MOSTLY EMPTY GETTING BETTER
- Still A Few Rocks
- Intestine Mostly Empty
- Intestine Still Stretched But Not As Bad
- Nerves Starting To Have Feelings Again

INTESTINE GETTING TOO FULL
- Muscle Thick And Strong Again
- Waste Not Too Big
- Nerves Give Good Warnings

BACK TO NORMAL—AN INTESTINE THAT WORKS

M.D. LEVINE MD
Encopresis

- See primary care doctor or GI specialist
- Evaluate for constipation or other causes
- Treatment: bowel cleanout, disimpaction, maintenance therapy
- Toilet training (initial or retraining bowels)
- Behavioral techniques to reduce fecal retention
- Dietary changes/exercise
Sleep

Major issues/causes/help!

- Sleep onset vs staying asleep
- Restless Leg Syndrome
- Medication Side Effects
- Pain
- Sleep Routine
- Behavioral Intervention
- Sensory Interventions-weighted blanket, soothing music
- Melatonin
- Medications: Clonidine; Trazadone

Mombie (n): someone resembling a living person, characterized by a staggering walk and a blank stare. Caused by having 1 or more children. Unlike a zombie in search of brains, the mombie is usually in search of a cup of coffee or a glass of wine.

FB/The Kid Chronicles
Behavior and Medical Conditions

- People with ASD get sick like everyone else—everything is not always related to autism (sometimes doctors have to be reminded of that!)

- Sudden or insidious change in energy, sleep, bowel habits, appetite, agitation, irritability  SEE HEALTH PROVIDER!

- IF person with ASD is resistant but ill—sedation may be necessary even for diagnosis

- Pain (dental, ear, GI, other)

- Check skin for rashes, infection, bug bites

- Chronic Medical Problems—diabetes, thyroid disease, heart disease, cancer etc
ASD symptoms can cause medical problems

- Self-Injurious Behavior (SIB) - real harm and self injury
- Pica (eating non-nutritive substances) - choking, bezoar
- Lack of safety awareness - traumatic injury
- Mental health issues
- Suicide
- Household accidents
- Victimization aggression of others
Complementary Alternative Therapies (CAM)
Examples of Complementary-Alternative in the treatment of ASD

<table>
<thead>
<tr>
<th>No benefit</th>
<th>Possible benefit, potential risk</th>
<th>Unknown benefit, potential risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretin</td>
<td>Facilitated communication</td>
<td>Possible benefit, low risk</td>
</tr>
<tr>
<td>Gluten-free casein-free diet*</td>
<td>Music therapy Melatonin Oxytocin Therapeutic horseback riding Other types of animal/pet therapy Sulforaphane Transcranial magnetic stimulation Yoga Body work (eg, massage/qigong) Energy therapies (eg, healing touch, Reiki) Biofeedback/neurofeedback Hypnotherapy Vitamin C Vitamin B12</td>
<td></td>
</tr>
<tr>
<td>Intravenous immunoglobulin Chelation Hyperbaric oxygen therapy Antimicrobial agents Vitamin B6 and magnesium Vitamin A Homeopathy Vagus nerve stimulation Stem cell therapy</td>
<td>Auditory integration therapy Omega 3 fatty acids Probiotics Oxidative therapies other than vitamin C (eg, methylcobalamin, folate, N-acetylcysteine) Zinc Interactive metronome Herbal products Amino acids (eg, taurine, dimethylglycine) Digestive enzymes Mindfulness therapy Acupuncture Craniosacral manipulation Chiropractic</td>
<td></td>
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</tbody>
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CAM-considerations

- Is based on overly simplified scientific theories
- Is claimed to be effective for multiple, different, unrelated conditions or symptoms
- Is claimed to result in a dramatic response or even a cure
- Is supported by case reports or anecdotal data rather than carefully designed studies
- Is not supported by peer-reviewed references, or the treatment's supporters deny the need for controlled studies
- Is said to have no potential or reported adverse events
- Healthy lifestyle: AAP “A healthy lifestyle is encouraged for children with ASD, as for all children. This includes a healthy diet (including adequate intake of essential nutrients), regular exercise, adequate sleep, management of stress, social support, and avoidance of neurotoxins”
ASD Outcomes

- Factors that have been associated with less favorable outcomes include:
  - Lack of joint attention by four years of age
  - Lack of functional speech by five years of age
  - IQ $<70$
  - Seizures or other comorbid medical or neurodevelopmental conditions
  - Severe ASD symptoms
ASD Outcomes

Factors that have been associated with positive outcomes include:

- Presence of joint attention
- Functional play skills
- Higher cognitive abilities
- Decreased severity of ASD symptoms
- Early identification
- Involvement in intervention
- A move toward inclusion with typical peers