Autism Spectrum Disorders: Medical Issues and Management

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September 2017
Disclosures

None
Goals

• Discuss Medical Evaluation of child with ASD
  – Examination
  – Lab and other testing
  – Understand comorbid diseases
    • Neurological
    • Sleep
    • Gastroenterological
    • Bone
Clinical Facts

• Clinical heterogeneity
  – ASD is a clinical diagnosis
• Intellectual Disability – 60-70%
• Language impairment - 30%

• Kasari et al. Autism Research 2013
Medical Evaluation and Exam

• Goals
  – Identify genetic disorders
  – Identify concurrent diseases
Genetics and Environment

- Twins
  - Monozygotic have almost 70% concordance (Frazier 2014)
  - Dizygotic have 36% for same sex twins and 18% for boy/girl twins
  - Identical twins are more likely to have similar level of ASD symptoms.
    - High levels of autism symptoms are genetic in origin. Less severe symptoms are not as likely to be inherited.
    - A shared environment played no "significant" role in the development of extreme autism symptoms in twins.
    - Problems in two separate areas – social communication skills and repetitive behaviors – are driven by the same gene or genes.

- Sibling rates : 5-20%
  - Higher if two sibs with ASD- 33%

- Male: Female ratio 5:1

- Ozonoff et al Pediatrics 2011
Genetics

• Testing
  – Karyotyping
  – Chromosome Micro Array- Comparative Genomic Hybridization
    • Measures duplications or deletions >1kB
      – Limits: Point mutations and microdeletions
  – FISH
  – Whole Genome
  – Whole Exome

From: My46.org
Genetic Disorders

- 20-25% with identifiable cause
- 3-5% single gene disorder
- Fragile X- 20+% with ASD
- Tuberous sclerosis 17%–60% with ASD
- Down Syndrome- up to 20% with ASD
- Neurofibromatosis, Angelman, dup15, Sotos, NF1, Smith-Lemli-Opitz Syndromes (most), Duchenne, 16p, PTEN, Shank3-Phelan McDermid Syndrome (>94%), Smith Magenis Syndrome (70%)
- Rett Syndrome
- Video courtesy of Margaret Bauman, MD
Genetic Testing Recommendations

- American College of Human Genetics
  - Detailed three generation family history
  - Detailed exam for syndrome identification
  - CMA for all
    - Fragile X - boys
    - MECP2 – girls
    - PTEN if macrocephaly

Why Test?

- Identification of single gene disorder
- Identification of newer genetic syndrome
- Help phenotype newer genetic syndrome
- Genetic diagnosis might lead to pathogenesis
- Possible treatment trials
- Family planning
Specific Exam Findings

• Head Circumference
  – Sotos, PTEN, Rett, Angelman, 16p11.2, Phelan McDermid 22q13.3,

• Muscle Tone/ motor
  – Angelman, Phelan McDermid, Mitochondrial, Rett

• Woods lamp
  – Neurofibromatosis, Tuberous Sclerosis
Testing: EEG

- Routine EEG abnormalities – up to 66% of ASD (Mulligan and Trauner, JADD 2014)
- Routine testing not recommended for all
- Overnight EEG for language regression- ESES
Testing: MRI

- Not recommended for ASD alone
- Abnormal neurological examination
- Focal seizure
- Head size

- Getting a child in scanner
- Scanner sounds: [https://www.youtube.com/watch?v=9GZvd_4ot04](https://www.youtube.com/watch?v=9GZvd_4ot04)
- MRI social story: [http://nmr.mgh.harvard.edu/transcend/kid_mri.html](http://nmr.mgh.harvard.edu/transcend/kid_mri.html)
When to do further testing?

- Dysmorphism, macrocephaly- child doesn’t look like parents
- Regression after age 3
  - Loss of developmental milestones
  - Loss of skills : ADL’s
  - Increased self stimulation/ self injurious behaviors
- Failure to make progress after a year
  - Developmentally appropriate, individualized program
- Other concerning history
  - Seizures
Sleep

• Most frequent complaint of parents of ASD children
• 53-83% of children with ASD
• More common than other psychiatric disorders

• Disorders of:
  – Sleep onset
  – Maintaining sleep
    • More frequent awakenings
  – Early morning awakening
Sleep

- No differences noted in ASD subtypes
- Strong behavioral component around learning to sleep
- Subjective findings lead to increase in ASD behaviors and irritability
  
Sleep Disorders

- **Etiology:**
  - Core deficits of ASD:
    - Behavior
    - Anxiety
    - Inflexible routine
    - Self regulation
    - Challenges with limit setting
  - Typical childhood sleep disorders
    - Restless leg syndrome
    - Obstructive sleep apnea
Sleep Disorders

- Concurrent medical disorders
  - Epilepsy
  - Gastro-intestinal disease
- Psychiatric comorbidities
  - Anxiety
  - Mood disorders
- Pain
Sleep Disorders - Cause

- Biological
  - Circadian rhythms
  - Melatonin dysregulation
    - Genetic findings
    - Metabolic findings
Treatments: Behavioral

- Establishing a Sleep Routine
- Provide a comfortable sleep environment
  - Temperature
  - Clothing textures
- Establish consistent bedtime routines
  - 4-6 bedtime activities
- Maintain a regular schedule
- Teaching your child to fall asleep alone in his/her bed
  - Gate or bell to alert parents that child is leaving room
Sleep Treatments

- Avoid naps in older children
- Daytime activities to improve sleep
  - Exercise
- Reward good behaviors
  - Privilege
  - Sticker
  - Other
Sleep Treatments

- Behavioral
  - Autism Speaks Toolkits
  - Sleep routine: training in bedroom
  - Bedtime pass

![Bedtime pass](image)
Sleep

• Medical
  – Ensure no medications which impair sleep
    • Caffeine
    • Stimulants
  – Melatonin (1-6 mg)- short or long acting
  – Clonidine (0.05-0.2 mg)- short or long acting
  – Guanfacine (0.5 -1 mg)-short or long acting
  – Trazodone (25-100 mg)
  – Others- diphenhydramine
  – Medication for comorbid illness…
Motor

- Motor delays
  - Gross motor- walk, sit
  - Fine motor- imitation
  - Dyspraxia
- Repetitive behaviors
  - No specific treatment
- Gait
  - Toe walking
- Hypotonia- low tone
- Catatonia
Epilepsy

- Rate in ASD is 2.4-19-37% (Amiet 2013-Kohane et al 2012, Yasuhura 2010, Thomas et al 2016)
- Variation depends on
  - Age: bimodal: 0-5 year old, Adolescence-Adult
  - Intellectual disability -24 vs. 8 % (Amiet’s Meta-Analysis 2008)
  - Females vs. Males – 34 vs. 18.5 % (Amiet 2008)
  - Etiology
  - Regression
  - Subtype of ASD (DSM IV)
  - Simplex vs. Multiplex (Amiet 2013)
  - Other- prematurity, low SES and speech problems (Thomas 2016),
Epilepsy

- There is no one seizure type in autism
  - Febrile, Benign, Focal and Generalized
- There is no one typical EEG in autism
- Staring Spells look like seizures
  - Use videos to help diagnose
Epileptiform discharges in ASD

- Epileptiform discharges (ED), found primarily during sleep, are present in the majority of children with autism.

- Are discharges associated with behavior changes/regression?
  - Tuchman and Rapin (1997): 59% with ED. 14% vs. 6% of autistic regression in the group with ED than in the group without ED
  - Rossi (1995): 18.9% ED but not associated with regression
  - Chez (2006): 60.7% with abnormality in sleep. No association with regression
  - Mulligan and Trauner (2014): 59.4% with ED
    - 95% of those with Sz had interictal ED.
    - 60% had ED during sleep. 3.6% with ED awake only. 20% of those with HFA
    - (Trauner 2014 https://doi.org/10.1016/j.yebeh.2014.10.020)
Behavioral correlates of ED

- Worse behavior / aggression (Turk et al 2009, Lee 2011)
- Increased aggressions (Mulligan and Trauner 2014)
- Increased stereotypies (Mulligan and Trauner 2014)
- Worse sleep (Mulligan and Trauner 2014)
- Worse motor skills, Attention, (SIB) in ID and non ID population (Viscidi et al 2013)
Role of treatment of ED

- No large scale controlled studies treating ED yet
- Chez (2006) treated 176 with VPA and EEG’s normalized.
  - No behavioral testing was done.
  - 2010- in 27 children. controlled trial without EEG for inclusion.
- Randomized controlled study is still needed.
Evidence for Causation

- Can ASD cause epilepsy?
  - No evidence. Association is not causation.
- Underlying brain mechanisms which predispose to both
  - YES! Genetic conditions, metabolic/mitochondrial conditions
- Can epilepsy cause ASD?
  - Increase rate in children with sz <2 (Clarke 2005)
  - Tuberous sclerosis lesions in L temporal lobe (Numis/Thiele 2011)
  - Landau Kleffner loss language
  - Swedish sibling study-
    - increased risk of ASD in children with epilepsy.
    - Increased risk of ASD in sibs and offspring of those with epilepsy
Role of EEG

• Epileptiform discharges, found primarily during sleep, are present in the majority of children with autism. (Mulligan and Trauner 2014, Chez 2009)

• Magnetoencephalography (MEG)
  
  • noninvasive
  • utilizes neurophysiological and magnetic resonance imaging paradigms to identify areas of abnormal activity in the brain.
  
  • may be more sensitive than routine EEG and possibly better able to detect abnormalities than 24-hour EEGs
  
  • In ASD - areas of persistent epileptiform discharges primarily in the perisylvian regions
Epilepsy Treatments

• Medications
  – No special medications for autism
  – Increase irritability – levetiracitam
  – Pyridoxine- 100 -200 mg BID

• Diet
  – Ketogenic diet
  – Low Glycemic Index diet

• Surgery
• VNS
• CBD
Gastrointestinal

- Common: 9-91%
  - Outpatients
  - Inpatients
    - 0.83% of pediatric and young adults with ASD vs. 0.54% typical general hospital with IBD (Kohane et al 2012)
- Gluten and Casein Free Diet
  - Controversy… still
- Restricted diets
GI consensus
Journal of Pediatrics January 2010 Supplements

• GI conditions that are common are also common in ASD
  - Chronic constipation
  - Abdominal pain +/- diarrhea
  - Gastro-esophageal reflux
  - Disaccharidase deficiencies
  - Inflammation of the GI tract
  - Pancreatic insufficiency

• Presentation as non GI disorder
  - 52% with disturbed sleep (vs 7% siblings)
  - Children with reflux esophagitis are more irritable than those who don’t (43% vs 13%)
  - Behaviors may be markers of abdominal pain or discomfort.
GI Issues

• Nutritional disorders
  – Vitamin deficiencies: C, D
  – Protein intake

Joanna
Pain Expression - Behaviors

- Pain looks different in each child
- Nonverbal children express pain nonverbally
- Child is more autistic…
• Vocal:
  – Screaming,
  – Verbal tics
  – Throat clearing, swallowing
  – Echolalia or scripted speech referring to
    • body parts, doctors, or pain
  – Moaning
  – Sobbing/crying without reason
  – Aggressive vocalization
• Behavior
  – Irritability
  – Sleep disorder
  – Non-compliance
  – Self injurious behaviors
• Body Movements
  – Facial Expressions
  – Dystonia
  – Mouthing
  – Gait change
  – Posture change
  – Tics
  – Dyskinesia
Autism and Bone?

- Children with ASD have high prevalence rates of conditions known to affect peak bone mass:
  - Gastrointestinal issues
  - Nutritional inadequacies
  - Low muscle tone
  - Decreased exercise
  - Medication usage
  - Metabolic and hormonal differences
Bone Development

Adolescence: Time of Marked ↑ in Bone Mass Accrual → Peak Bone Mass

For optimal peak bone mass, normal bone mass accrual in adolescence is necessary.
What about Fractures?

- When evaluating Emergency Room visits of a national database (NEDS 2011):
  - Higher OR of hip fractures in Children and Adults with ASD
  - Higher OR for forearm and spine fractures in women ages 23-50 with ASD

Neumeyer et al., 2015
Other Medical Issues

- Obesity
  - Metabolic syndrome
  - 2-3x increase prevalence in ASD and Trisomy 21

- ENT-
  - 1 in 6 has PE tube placement in US
  - Increased prevalence of Obstructive Sleep Apnea

- ENT: Ackerman et al. 2012
- Obesity: Rimmer et al 2010
Other Medical Issues

- Drug Reactions
- Endocrine Conditions
  - Pre Menstrual Syndrome
  - Onset of adolescence
Research at The Lurie Center

- Autism biomarker study – Children’s Autism Metabolome Project (CAMP) for children under 4
- Sidekick study- To evaluate the efficacy of Affinities Therapy, a therapy model for verbal children 6-11.5
- Roche Vasopressin analog study for Children- coming soon
- Neuro-inflammation Study- adults
- Angelman Syndrome treatment study
The Lurie Center

Mission

Our goal is to advance knowledge of autism spectrum and related disorders and to rapidly translate discovery into exceptional care over a lifetime.

Multidisciplinary clinic for children and adults with autism and developmental disabilities

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Thank you!