Autism Spectrum Disorders: Medical Issues and Management

Ann M Neumeyer, MD

September 2017

LURIE CENTER FOR AUTISM

MASSACHUSETTS GENERAL HOSPITAL

MassGeneral Hospital *for* Children℠

Disclosures

None

Goals

- Discuss Medical Evaluation of child with ASD
  - Examination
  - Lab and other testing
  - Understand comorbid diseases
    - Neurological
    - Sleep
    - Gastroenterological
    - Bone

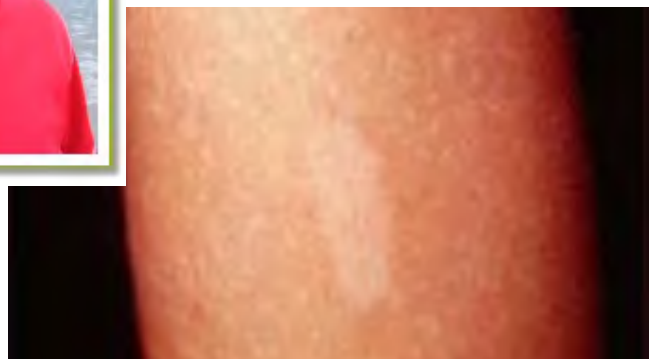
Clinical Facts

- 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

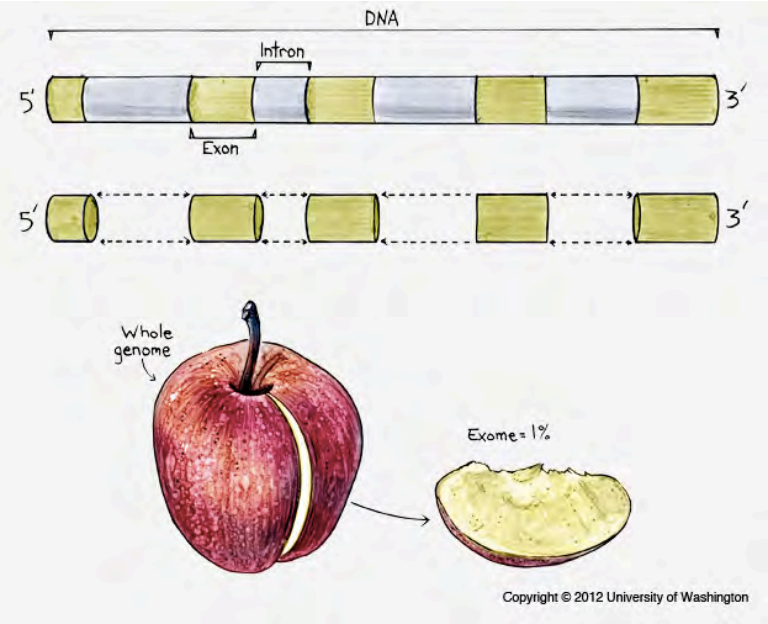


Genetics and Environment

- 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

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children

- 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

- Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med 2013;15:404

Why Test?

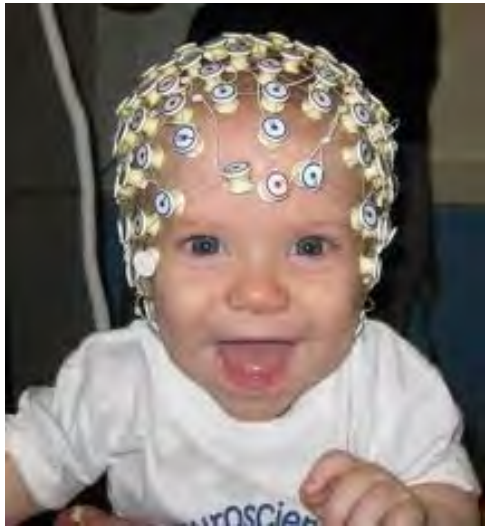
- Identification of single gene disorder
- Identification of newer genetic syndrome
- Help phenotype newer genetic syndrome
- Genetic diagnosis might lead to pathogenesis
- Possible treatment trials
- Family planning

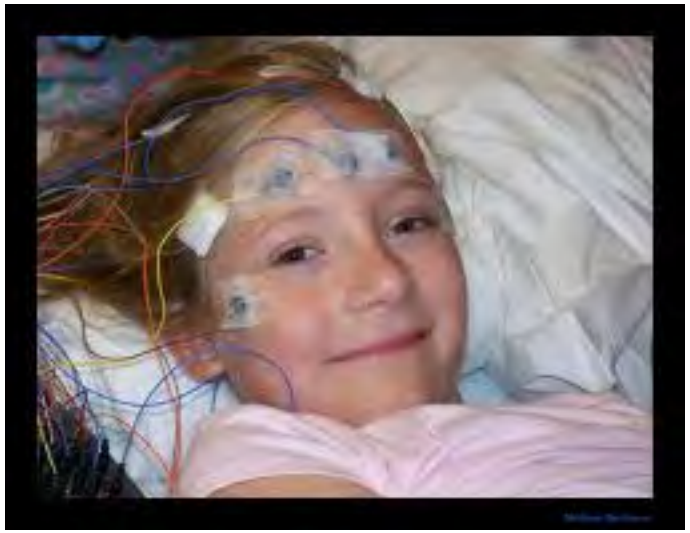
Specific Exam Findings

- Head Circumerence
  - 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

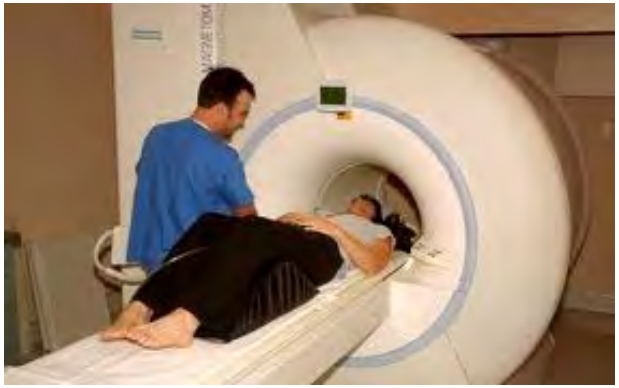
- Routine EEG abnormalities – up to 66% of ASD (Mulligan and Trauner , JADD 2014)
- Routine testing not recommended for all
- Overnight EEG for language regression- ESES
- https://www.autismspeaks.org/science/resources-programs/autism-treatment-network/atn-air-p-eeg-guides





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
- MRI social story: 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

- Shreck et al (2004)

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

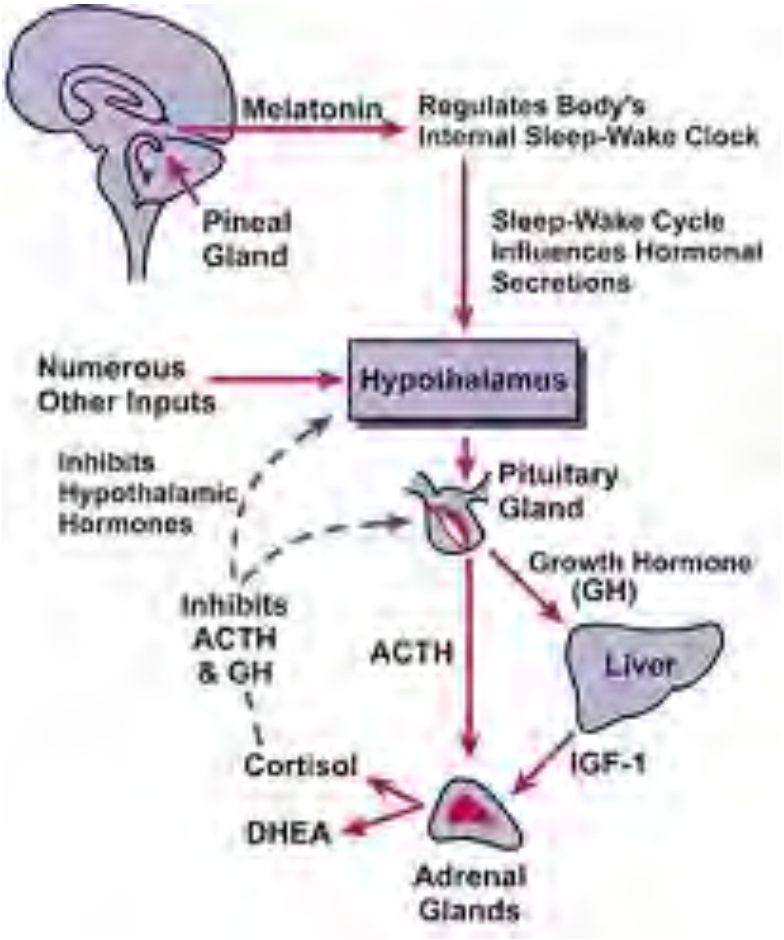
Sleep Disorders

- 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

  - Melke et al (2009)



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

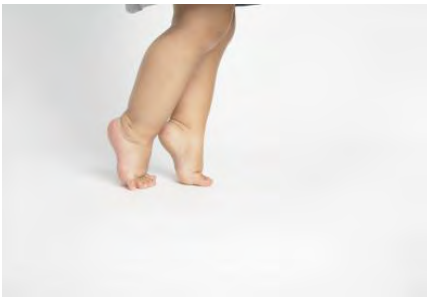
- Behavioral
  - Autism Speaks Toolkits
  - Sleep routine: training in bedroom
  - Bedtime pass
  - https://www.autismspeaks.org/science/resources-programs/autism-treatment-network/tools-you-can-use/sleep-tool-kit

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

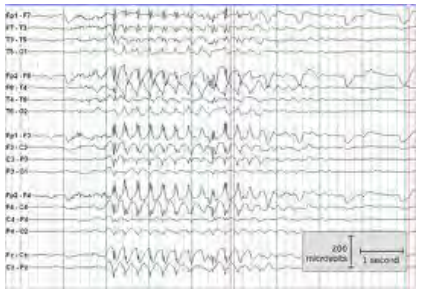


Epilepsy

- 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

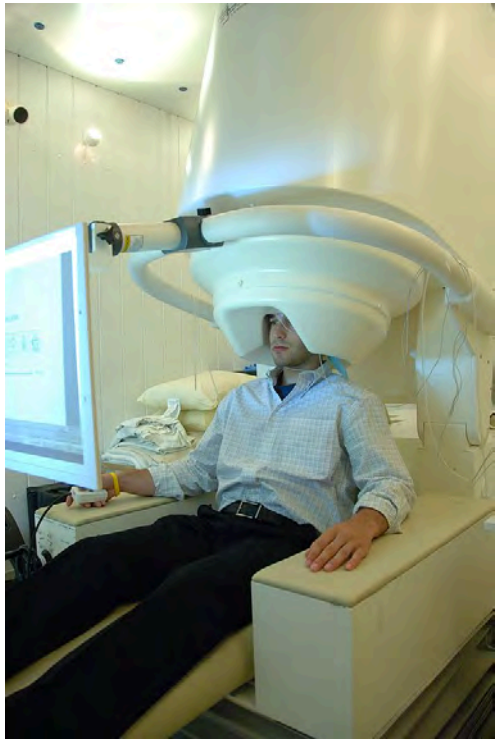
- No large scale controlled studies treating ED yet
- Chez (2006) treated 176 with VPA and EEG's normalized.
  - No behavioral testing was done.
- Hollander (2001) –open trial with VPA improved aggression.
  - 2010- in 27 children. controlled trial without EEG for inclusion.
- Randomized controlled study 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

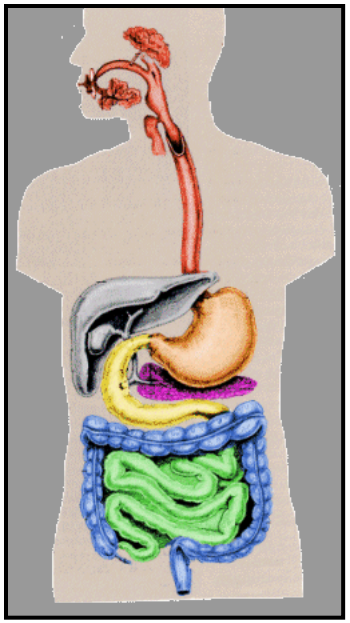


Epilepsy Treatments

- 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

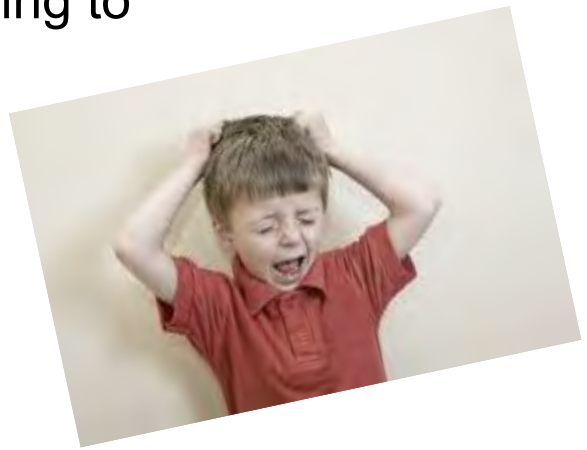
- Buie et al, 2010, Hurwitz, 2013, Whiteley, 2014

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



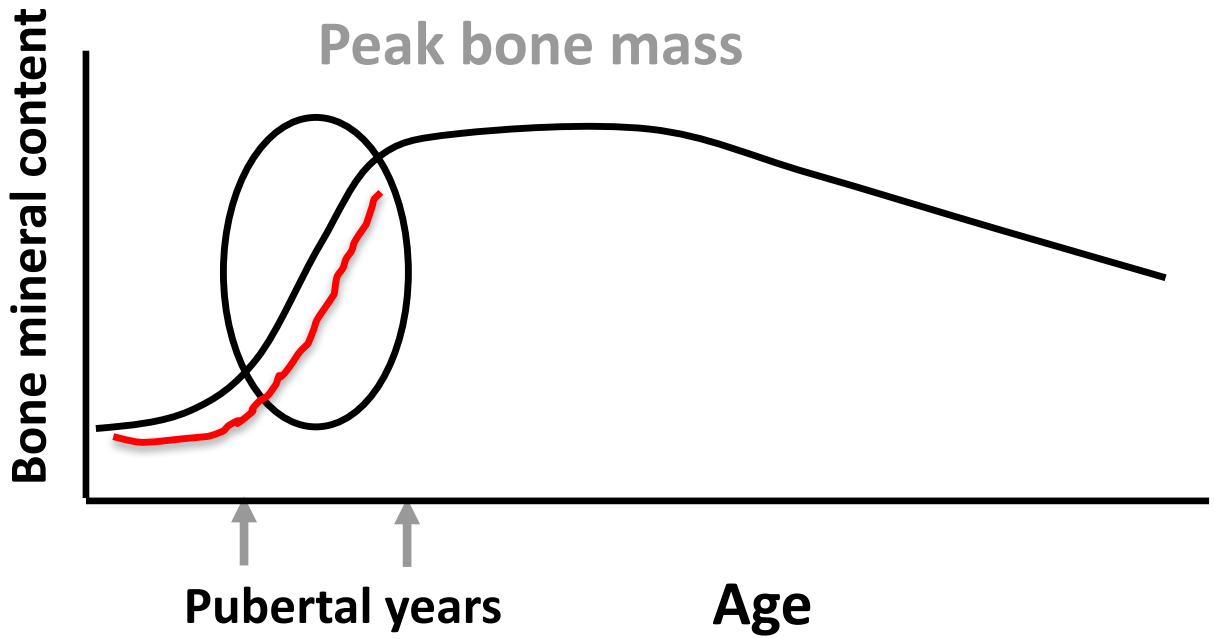
- Behavior
  - Irritability
  - Sleep disorder
  - Non-compliance
  - Self injurious behaviors
- Body Movements
  - Facial Expressions
  - Dystonia
  - Mouthing
  - Gait change
  - Posture change
  - Tics
  - Dyskinesia

Autism and Bone?

- Children with ASD have high prevalence rates of conditions know 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

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children

- 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

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children

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

ANeumeyer@MGH.harvard.edu

Thank you!