


Aging Wisely With Autism

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Disclosures

- A Parent
- Long term Autism Advocate
- Employer of Eden Adults
- Extensive experience providing healthcare to adults with complex autoimmune disorders
- Researcher on the multidisciplinary team at The Seaver Center for Research and Treatment at the Icahn Mount Sinai School of Medicine



Timeline

- 1943. Autism gets a name (Kanner)
- 1967. Bruno Bettelheim. Autism results from an unstimulating environment
- 1967. Bernard Rimland. The Autism Research Institute
- 1971. Autism is not Schizophrenia (Kolvin)
- 1980. Autism in DSM-3
- 1985. Theory of Mind (Frith)
- 1987. Ivar Lovaas. ABA Introduced
- 1988. Candida Infection (Rimland)
- 1991. Impaired Executive Function (Ozonoff)
- 1994. PDD-NOS, Aspergers added to DSM-4



Timeline

- 1996. Temple Grandin. Thinking in Pictures
- 1997. Neuroinflammation?? (Hollander, Del Giudice-Asch et al)
- 1998. MMR Vaccine (A. Wakefield)
- 1999. Genomic screen (Risch et al), Mitochondrial function (Lombard)
- 2000. THERE IS NOT ONE CAUSE
- 2003. Courchesne. Rapid brain growth
- 2004-2012. Genetic vulnerability and Environmental susceptibility
- 2013. DSM-5, new diagnostic criteria
- 2013. Vaccines not a risk
- 2013-2019. Biomedical abnormalities. ASD Children have undiagnosed medical conditions
- 2019. AUTISM IN ADULTHOOD, launches

B lymphocyte antigen D8/17 and repetitive behaviors in autism.

Hollander E, et al. Am J Psychiatry. 1999.

Authors

Hollander E¹, DeGiudice-Asch G, Simon L, Schneider J, Carlsright C, DeCaria CM, Kwon J, Cunningham-Rundles C, Chapman F, Zelnick J.B.

Author information

¹ Department of Psychiatry and the Seaver Autism Research Center, Mt. Sinai School of Medicine, New York, NY 10029-6574, USA. e_hollander@mtsinai.mssm.edu

Citation

Am J Psychiatry. 1999 Feb;156(2):317-20.

Journal of Autism and Developmental Disorders
April 1999, Volume 29, Issue 2, pp 137-169 | [Cite as](#)

Brief Report: A Pilot Open Clinical Trial of Intravenous Immunoglobulin in Childhood Autism

Authors Authors and affiliations

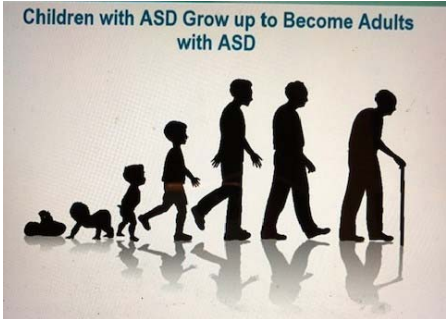
Gina DeGiudice-Asch, Lorraine Simon, James Schneider, Charlotte Cunningham-Rundles, Eric Hollander

The Health Burden of Kids and Young Adults with Autism

Kohane et al 2012

- Detailed assessment of 15,000 EMR conducted by the US Centers for Disease Control and Prevention
- The comorbidities in ASD require multidisciplinary management
 - Eczema,
 - Allergies and asthma
 - Ear and respiratory infections
 - Gastrointestinal problems
 - Headaches
 - Seizures

Children with ASD Grow up to Become Adults with ASD



Overview of Presentation

- Most adults spend ¾ of their lives as adults
- Less than 2% of ASD research funds are spent on adult research
- Communication among health care providers is complex but ESSENTIAL to ensure the best care for our patients
- Our job in caring for ASD Adults is to THINK OUT OF THE BOX . The co-occurring conditions .
- Dr Kartoz: Health Service Provisions and Appropriate Medical Care
- Dr Froncek: Information/Misinformation and Immunology

Public Health Dilemma

- Autism is Heterogeneous
- What is the Natural History of Aging in Autism ?
- What are the systemic co-occurring medical conditions in adults with ASD?
- What is the Natural History of the co-occurring medical and psychiatric disorders among adults with autism ?
- Do the co-occurring conditions tell us about the biologic pathways of ASD?
- How can the co-occurring conditions aid in the detection of ASD?

2015. First Large Retrospective Study

The health status of adults on the autism spectrum.

Croen LA, et al. Autism. 2015.

Authors:
Croen LA¹, Ziebu CP², Qian YF³, Massadeh ML⁴, Ruan SF¹, Solway SF¹, Kripke CF¹.

Author information

- 1 Kaiser Permanente Northern California, Oakland, USA Link A.Croen@kp.org
- 2 Kaiser Permanente Northern California, Oakland, USA
- 3 Kaiser Permanente Northern California-Dante Ross, USA
- 4 University of California, San Francisco, USA.

Citation:
Autism. 2015 Oct 18;17(1):14-23. doi: 10.1177/136228131557517. Epub 2015 Apr 24.

Abstract:
Compared to the general pediatric population, children with autism have higher rates of co-occurring medical and psychiatric illnesses, yet very little is known about the general health status of adults with autism. The objective of this study was to describe the frequency of psychiatric and medical conditions among a large, diverse, insured population of adults with

- Adults 18 + years
- 2008-2012
- ASD 2,108/controls 21,080
- Health status , based on ICD-9 codes
- Mean age 32
- Males 67% ;Females 33%
- KP health program 8000 docs, 3.5 million pts

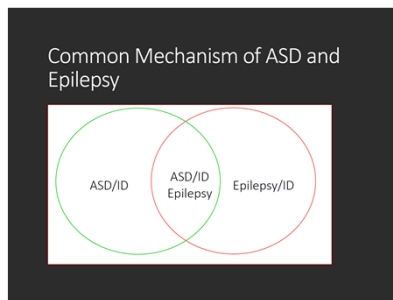
Findings of Croen et al .2015

- Individuals with ASD Have a higher burden of medical and psychiatric conditions than individuals without ASD
- Medical Conditions : Seizures: 12% vs 1%, GI :47% vs 38%, Sleep 19% vs 10%, HTN 27% vs 19%, HLD 26% vs 18%
- Psychiatric Conditions: Depression 38% vs 17%, Anxiety 39% vs 18%,Bipolar 30% vs 9%
- GOOD News : no Tobacco, little ETOH, Less Cancer
- Co-occurring conditions cluster together :
 - Sleep and GI
 - Feeding and Speech
 - Diabetes and Cardiovascular ds
 - Dementia and Parkinsons

Autism isn't a Stand Alone Disorder:

- 2011: Cleveland Clinic, EMR 2005-2008: Sz, HLD, GI
- 2014: Hsieh et al, EMR, Obesity in ID, Downs > ASD
- 2016: U Wisconsin, Thyroid ds, Neuro ds, CVS
- 2016: Cashin, Australia, ASD Adults more at risk
- 2017: JHU, Challenging behaviors decline, BMI >30, Sz, GI
- 2018: ASU, 4 year looking at behavioral predictors of cognitive decline
- 2018: Scotland, Blindness, Deafness, ID

ASD Coexists with Epilepsy



Neuro 101

- The brain transmits electrical impulses from nerve cell to nerve cell.
- When a seizure occurs there is an ABRUPT change in the brain's electrical rhythm. Nerve cells cannot function normally, Loss of synchrony occurs. Abnormal Rhythms.
- What WE SEE: abnormal rhythmic movements of arms, legs, face. Loss of consciousness, dangerous if >5 minutes. Everyone should have a plan for > 5 minutes
- Epilepsy diagnosis : 2 unprovoked seizures of any type



Epilepsy In ASD

- Prevalence: 20-40%, Increases with Age
- ILAE 2017, Classification of Seizures. Generalized and Focal/Partial
- All types of seizures can occur . Generalized Tonic-Clonic : entire brain abnormal electrical activity
- LOOKS CAN BE DECEIVING : Focal Impaired Awareness
=Complex Partial Seizures: behavioral changes, staring ahead, eye deviation, eye fluttering
- Associated increase in Mortality

Epilepsy in ASD

- Diagnosis : Extended EEG
- Subclinical Electrical Discharges (SED). To treat or not to treat ???
- Causes: Genetic and Metabolic Syndromes. Idiopathic
- Heath Factors that can affect seizure control:
 - Sleep
 - Fever
 - Dehydration
 - Allergies
 - Dietary factors
 - Psychological Stress

Consequences of Epilepsy

- SUDEP
- Neurologic : immediate and permanent damage
- Injuries: falls, fractures
- Anxiety and Depression
- Medications: need to maintain a high AED level , individualize the therapy

Treatment of Epilepsy in ASD

- | | |
|--|--|
| <ul style="list-style-type: none"> • Antiepileptic Drugs (AED): Surveillance <ul style="list-style-type: none"> • Depakote (Valproate) • Lamictal (Lamotrigene) • Keppra (Levetiracetam) • Trileptal (Oxcarbazepine) • Topamax (Topiramate) • Vimpat (Lacosamide) • Tegretol (Carbamazepine) • Klonopin (Clonazepam) | <ul style="list-style-type: none"> • Balancing Tolerability and Effectiveness: Side Effects <ul style="list-style-type: none"> • Cognition • Vertigo • Behavioral changes • Weight gain • Weight loss • Severe rash • Hyponatremia • Headaches • Tremor • Ataxia |
|--|--|

Link between ASD and Parkinsons Disease (PD)

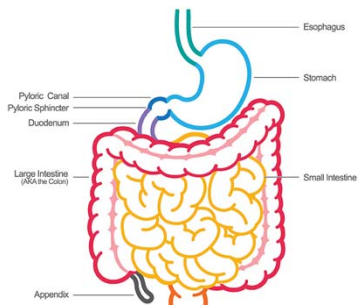
- Hollander ,2009. Neurologic Considerations : Autism and Parkinson's Disease. Repetitive Behavior of a Compulsive-Impulsive Nature
- Piven, 2015: Higher frequency of parkinsonism and PD among ASD adults older than 30 years . Patients were excluded if on neuroleptic medications. Rate in general population 0.9%, 20% and 27% in the study .
Questions : do the neuroleptic drugs unmask a pre-clinical stage of PD? Do ASD and PD share a common pathogenic mechanism ?

Sleep Wake Cycle Irregularities:



Sleep Disorders in ASD

- Insomnia
- Increased Sleep Latency
- Nighttime Awakenings
- Abnormal Melatonin Physiology: Melatonin is a powerful antioxidant that regulates sleep and Neuroplasticity. Deficits of Melatonin in ASD, ASMT gene deficit in ASD A susceptibility gene? . Melke Molec Psych 2008; Torjman Int J med Sci 2013
- No Sleep: Mood variability, Inattention, Hyperactivity, Poor Social Interaction
- Complicated by GI Symptoms or Seizures ? Sleep Apnea
- Screen-Time



GI Disorders

- Gastroesophageal reflux (GERD), Constipation, Colitis, Ulcers, Food Intolerances : DIAGNOSTIC CHALLENGES
- Feeding and Nutrition issues in ASD. Do they result from Bowel Dysmotility, Dental diseases, Neural sensory sensitivities?? Restrictive pattern, Overeating, Motor Issues with chewing and swallowing, Pica
- No higher rates of celiac ds in ASD
- Gluten sensitivity 5-8% general population, 20-25% ASD
- The Microbiome : THE New Frontier

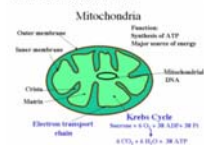
Abnormal Bacterial Gut Flora

- We coexist with 100 trillion microbial cells: Symbiotic and Pathogenic . Dysbiosis occurs: microbial metabolites produce neurotoxins , the gut peptide –brain association
- Associations exist between unhealthy states and an imbalance gut microbiota : Psoriasis, Systemic Lupus Erythematosus, IBD
- In ASD : see abnormal bacteria absent from healthy controls; translocation of bacterial species to parts of the GI tract that are not host to those bacteria in healthy controls (Finegold et al 2010; Ekiel et al 2010; Williams et al 2012)

Mitochondrial Dysfunction and ASD

Powerhouse of Cell

What are mitochondria?



Functions

- Produce 90% of energy to sustain life and organ function
- Regulate calcium levels
- Produce cell signaling molecules
- Controls Reactive Oxygen Species

Mitochondrial Dysfunction and ASD

Implicated in Psychiatric and Neurologic diseases

The Symptoms : Seizures, developmental Delays, GI Dysfunction, Multiorgan involvement

Mitochondrial dysfunction can unify the disparate clinical and physiologic findings associated with ASD.

Research studies:

- 2010, UC Davis, 80% children with ASD, blood tests indicate mitochondrial dysfunction
- Biochemical evidence of mitochondrial dysfunction in post-mortem brain tissue of adults and kids with ASD (Chauhan et al 2011; Tang et al 2013).
- Markers of mitochondrial dysfunction on brain MRI Spectroscopy scans of adults and kids with ASD (Goh et al 2014)

Animal Models of ASD demonstrate mitochondrial dysfunction (MacFabe et al 2007; Mac Fabe et al 2008; Thomas et al 2010)

Autonomic Nervous System in ASD

- ANS: innervates our organs and carries out bodily functions automatically (e.g. sweating, breathing, heart rate)
- Sympathetic NS: "fight or flight" response
- Elevated sympathetic activity frequent in kids and adults w/ ASD (Fan et al 2009; Cheshire 2012; Daluwitte et al 2012)
- Manipulation of ANS to treat aggression, anxiety, irritability in ASD adults. Propranolol improved impaired social interaction and communication (Zamzow et al, 2016)

NORMAL BONE



OSTEOPOROSIS

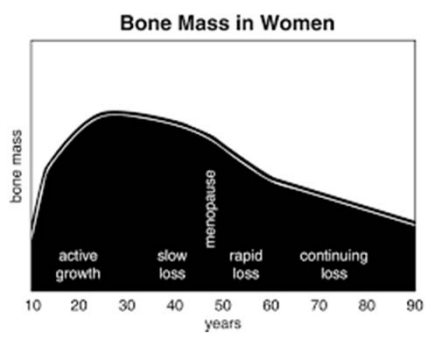


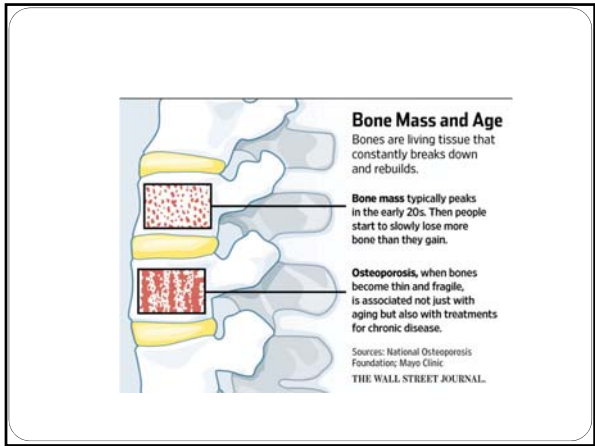
Osteoporosis

- Not just a disease of Middle Aged Women
- Important for children to achieve Peak Bone Mass
- Low Bone Mineral Density leads to increase risk of Fracture
- Risks: lack of physical exercise, diet restrictions, calcium and vitamin D intake, medications
- Bone metabolism abnormalities on DEXA scans in ASD and Increased risk for hip fractures in children and adults with ASD

- Heliger et al 2008
- Neumeyer et al, 2013
- Kocovska et al 2014
- Matano, 2011
- Neumeyer et al 2015



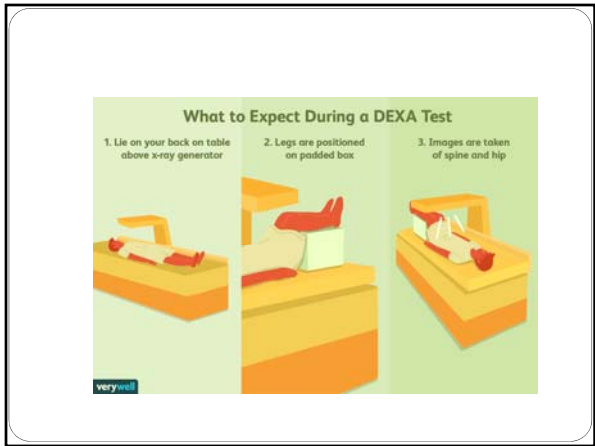





Bone Density in Young ASD Adults

Ekhaspour, et al J Autism Dev Disord 2016

- BMD in ASD individuals ages 14-21 was lower at the hip, femoral neck and spine in compared to controls seen on DEXA scans
- Decreased Bone Cortical Thickness seen on X Rays
- Did not examine association low BMD with diet, calcium, vitamin D or lack of physical activity
- Bone health evaluations should be routine care





ISCD
The International Society
For Clinical Densitometry
Official Position

Diagnosis of Osteoporosis

- T-score ≤ -2.5 at LS, TH, or FN
- In certain circumstances, the 33% (1/3) radius may be used
- Forearm BMD should be measured when
 - Hip and spine cannot be measured or interpreted
 - Hyperparathyroidism
 - Very obese patient exceeds weight limit of DXA table
- Application may vary according to local requirements


Shepherd JA et al. J Clin Densitom. 2015;18:274-286.

AED and Bone Mineral Density

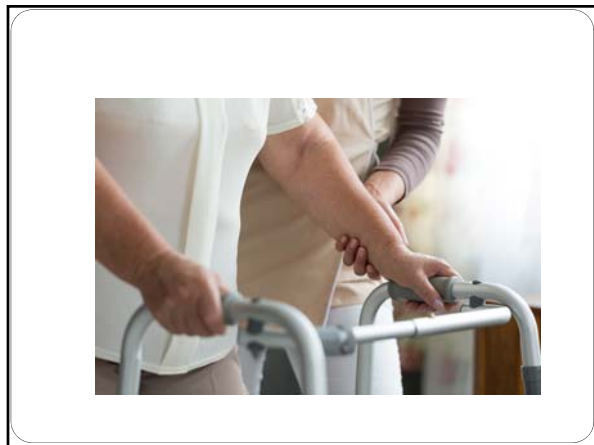
- Most studies on children. No mention of ASD
- Impact on Vitamin D metabolism and BMD
- Older AEDs and Levetiracetam as monotherapy suggest higher risk for low BMD. Beniczky SA et al Seizure 2012
- Long-term AED treatment with Valproate, Carbamazepine effect skeletal mineralization and lead to low BMD. Babayigit A et al Pediatr Neurol. 2006.

WE DON'T WANT THIS TO OCCUR!

Hip Fracture









FDA Approved Pharmacologic Treatment for Osteoporosis

- Anabolic Agents
 - Increase bone formation, increase bone mass, improve bone architecture
 - Teriparatide (Forteo)
 - Abaloparatide (Tymlos)
- Antiresorptive Agents
 - Lower bone mass, stabilize bone architecture
 - Bisphosphonates: Aledronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel), Zoledronic acid (Reclast)
 - RANK –L inhibitor: Denosumab

Autism Biology, Comorbidity, Mortality

- Higher risk of Premature Death is ASD
- 3 to 10 times higher than the General Population
- Bilder et al . 2012. Autism Spectrum Disorders: related to Epilepsy, Respiratory Conditions and ID
- Woolfenden et al. 2012. Dev Med & Child Neuro. Epilepsy highest risk for early mortality
- Guan J. Am J of Public Health. 2017 . Injury leading cause of death

2018. Health Problems in Decedents with ASD

Bishop et al. Autism Research 2018.

- A retrospective analysis using diagnostic codes to evaluate EHR in decedent adults with ASD (N=131) and community controls (N=16,981) who had died since 1979 from the Marshfield-Clinic U of Wisconsin
- ASD Adults died at age 56.1, Controls at age 75.2
- Findings: Increased risk of Epilepsy
 - Cardiovascular diseases: CHF, valve ds, xs clotting
- May not be representative of current ASD population
- Data obtained using diagnostic codes, may not be actual extent of health problems
- Still valuable given the growing population of ASD adults



Why People with Autism Die at a Younger Age ...

- British Journal of Psychiatry, January 2018.
- Between 1987 and 2009, Swedish researchers : chart analysis from the Swedish Health databases. For each ASD proband they pulled 100 controls matched by age, gender, county of residence in the year the ASD diagnosis was made . 27,000 ASD compared to 2.6 million without ASD
 - ASD with ID, life expectancy 39.5 versus 70 years in general population
 - ASD w/o ID, life expectancy 58 years
 - Leading causes of death : Heart Disease, Suicide, Epilepsy

What's Needed Next?: More of Everything

- Advocacy : Direct Health Assessments with Longitudinal Aging Studies
 - Address the barriers to accessing good care
 - Extend research focus to adulthood ASD
- Awareness : Comorbidity is to be expected in ASD
 - Regular Surveillance
 - Educate the practitioners who provide community-based services
 - Health Promotion

Aging Wisely with Autism: Prevention and Primary Care

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Associate Professor
The College of New Jersey
School of Nursing, Health and Exercise Science
Nurse Practitioner, Rheumatology Associates of Princeton

Prevention for the ages

- Objectives
 - Review prevention measures for young and older adults with autism
 - Discuss challenges to obtaining adequate care to accomplish the above

"Autism itself is not a cause of premature mortality. Rather, it relates to many of the medical and mental health conditions in this report – most of which are treatable and/or preventable."

<https://www.autismspeaks.org/sites/default/files/2018-09/autism-and-health-report.pdf>

Introduction

- Little is known about specific risks to health in adults with autism
- Primary care providers (unlike pediatricians) are not (YET) well educated on excellence in care for adults with autism
- One component of aging well is prevention/avoidance of disease
- Driving forces
 - Routine preventative care
- Risks for adults with autism
 - Integrating psychological and medical is essential (Hwang et al. 2017)
 - Life is already a challenge, a chronic illness will only make it more difficult
 - Social integration important (role of employment-Hwang)
- It's a family affair
- Finding a practice that will welcome adults with autism
- 'Exercise is medicine'

It's a Family Affair



Prevention versus Early Detection

- Prevention is ideal.
 - Prevention may also include DELAY of onset
- Early Detection
 - Screening so that disease can be caught early and treatment begun
 - Allows for planning, even if cures not available
 - 'be careful what you ask for' in early detection

Risks for Adults with Autism

- Related to disease
 - Osteoporosis
 - Seizure
 - Depression (14% Davignon, 2018)
 - Sleep
 - Obesity (25%)
 - Constipation/functional GI
- Related to meds
 - Diabetes (also disease)
 - High cholesterol
 - Wt gain
 - Periodontal disease
 - polypharmacy

“Risks” related to aging

- High blood pressure
 - 50% of people ages 55-64 (AHA, 2019)
- Diabetes
- Cancer
- Periodontal disease
 - 70% of 65 year olds (AAP, 2019)
- Osteoporosis
- Falls
- Obesity
 - 42.8% of 40-59 y/o v. 35.7 % of 20-39 y/ (CDC, 2019)

Osteoporosis
Seizure
Depression (14% Davignon, 2018)
Sleep
Obesity (25%)
Constipation/functional GI
Diabetes (also disease)
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Osteoporosis
Falls
Obesity
42.8% of 40-59 y/o v. 35.7 % of 20-39 y/ (CDC, 2019)
Diabetes
Periodontal Disease
Obesity
Osteoporosis

Routine Care for Adult

Note some is prevention/some is screening

- Ages 26-50
 - Annual BP monitoring
 - Flu shots
 - HPV vaccine if not already complete
 - Blood glucose monitoring IF meds, obesity (age 40)
 - Weight management
 - Sunscreen use
 - Vision issues (age 40)
 - Pap smear for Women if sexually active and contraceptive care
 - Folic acid in anyone who can potentially become pregnant
 - HIV testing

Routine Care (cont.)

- Ages 50-65
 - Colon cancer screening
 - Stool testing annually (FOBT FIT)
 - Colonoscopy every 10 years
 - Mammography
 - Every 2 years if average risk
 - High risk?—MRI,
 - Audiology
 - Statin use if 10 year risk of cardiovascular disease > 10 %
- Ages 65 and older
 - Pneumonia vaccine
 - Shingles vaccine
 - Falls prevention
 - Osteoporosis in women if not already done

Additional Prevention

- Avoid alcohol
- Avoid cigarettes
- Social integration/employment
- Healthy diet
- Exercise
 - 150 min per week
- Dental Care
 - Better grips with foam/big grip
 - Bend the toothbrush
 - Floss holders
 - Avoid items that allow sugar to 'stick' in the mouth

You are what you eat

- Some nutrients to consider for brain health
 - Nuts (if choking a concern: almond butter/nut butter; almond milk, bake with these butters/nuts)
 - Fish
 - Berries
 - Dark green leafy vegetables
 - Turmeric
- Diets to lower inflammation
 - Limit red meat
 - Limit simple sugars
 - Low fat/ Mediterranean
- Nutrients for metabolic health
 - Natural sugars
 - Cinnamon

Exercise is Medicine®

- Reduces risk for cardiovascular disease
 - Drops blood pressure, increases good cholesterol
- Reduces blood sugar and the risk of developing diabetes (by up to 50%)
- Helps reduce risk of depression
 - Just as effective as medication for mild-moderate depression
- Reduces inflammation
- Reduces risk of cancer
- Improves muscle strength/ reduces falls
- Helps normalize weight and prevents obesity
- Remember, 'sitting is the new smoking'

Exercise for adults with ASD

- Limited research
 - Benefits (Sorensen & Zarrett, 2014)
 - Decrease stereotype and repetitive behaviors
 - Improve cognition and social/emotional function
 - Challenges
 - Motor impairment, social skills and repetitive behaviors
 - Kids with ASD get less activity, adolescents even less, adults??
 - Opportunities
 - Parental exercise level best predictor of child exercise
 - Research on exercise suggests short bursts of activity beneficial

Exercise Best Practice

- Walking/Running/Swimming
 - Individual activities
- Individualize
 - Consider fitness trackers and other technology
 - Praise and + feedback
- Incorporate into regular activity
 - Take the stairs
 - Walk to the store/restaurant
- Consider PT and OT referrals
- Get creative

Finding a practice

- Adults with autism may have lower satisfaction with care (Nicolaidis, 2012; Gerber 2017)
 - Lower satisfaction leads to poorer adherence
 - And in the Nicolaidis study, lower rates of tetanus vaccine or a pap smear
- Barriers
 - Raymaker (2017)—fear/anxiety and sensory issues
- Education of providers may be lacking (Hwang et al., 2017)
- Look for a center
- Consider tele-health capabilities

Helpful hints for adult care

AASPIRE

Providers must do a thorough assessment of a patient's communication style

Processing time may be slower—will this provider take time?

Look for providers who can alter sensory experience

paper gowns are scratchy; lights too bright

Written information must be clear

Demonstration and Teachback

Information, Misinformation, and Immunology

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Assistant Clinical Professor of Medicine, Rutgers

Disclosures

- I am Uncle Doctor Mike.
- I take care of patients with autism and receive remuneration from their families and insurance companies.
- My office uses the Shred Doctors.
- I've been too busy seeing patients and fencing to do any research.

Part III

- Where to begin?



Outline

- How to get medical information and evaluate its quality
- How to decide what to do in the absence of perfect information
- Some stuff about immunology and the interface with autism

The Information Part

The Information Explosion

- In 2005, when I came to Princeton, there were 682,121 articles recorded in PubMed
- If I had read 2 articles per day that year, I would have been *9 centuries behind* in my reading by 2006.
- I didn't read 2 articles a day.

I didn't have these guys, either.



Sources of New Information

- Press reports: NYT, WSJ
- Key journals in field (mostly specialists)
- Review articles
- Pub Med search
 - On-line access restricted for many articles
- Cochrane reviews
 - 29 for autism

Evaluating a Study

without being a statistician

- Status of journal
- Impact factor = #citations/articles publ'd
- Peer review
- Primary literature > secondary
- Who funded the work?
- Methods, quality of data and its analysis, conclusions that fit the data

Barriers

- Influence of industry: funding, agenda
- Publication bias: favors +ve results
- Science not always the prime motive
 - FDA approval, establishing precedent
- Prior probability of an effect
 - If low, then a statistically significant result is still more likely a FALSE positive

Good methods

- Random, blinded allocation of patients
- Who is included, excluded, and why?
- Outcome measures clinically meaningful
- Few lost to FU compared w/ # bad outcomes (FU 80% or better)
- Blinding of observers and participants
- Objective, reproducible diagnostic stds.
- Big enough (power)

The Study You Want

- Large, multi-center, randomised, double-blind, placebo-controlled prospective study funded independently of industry and wherein all the patients are 100% adherent to their treatments and show up for 100% of their follow up visits and all the investigators follow all the protocols exactly and there are no problems with data analysis

Sorry

You're never gonna get it!



Often we have to settle for...

- Small studies
- Meta-analyses that include a lot of small studies
- Retrospective, association studies
 - Show association, not necessarily causation
- Unblinded or uncontrolled studies
- Industry funding that may influence what is published and what is not

Hierarchy of Study Designs

- Randomised controlled trial
- Controlled trial
- Prospective cohort study
- Retrospective cohort study
- Case-controlled study
- Cross-sectional study
- Survey



• Favors CAUSATION

• Favors CORRELATION

Correlation is not Causation

- In the spring and summer there is a high correlation between newly planted trees and the rate of growth of grass around them.
- Therefore, I will plant new trees in the spring so I can have a better lawn.
- YES?

Correlation is not Causation

- NO!
- The trees are NOT the cause for the grass growing fast.
- The cause is water and sunshine.
- The trees were planted at the same time to take advantage of these, hence the correlation.

Example: One of Many

- Study shows correlation between low homocysteine levels and cardiac events
- Doctors prescribe B vitamins and regularly check homocysteine levels to reduce their patients' risk
- Prospective study later shows doing this does not reduce cardiac disease

So what?



- How is the study biased?
 - What is the systematic error that might produce an erroneous conclusion?
- Can the study be generalised to other individuals?
- Is the study applicable to the specific person I'm concerned about?
- How can I use the results?

How'm I doin'?



The Immunology Part

Immunology and Autism

- Immune anomalies in individuals with ASD and their families
- Studies inconsistent and controversial
 - Small sample sizes
 - Inappropriate controls
 - No consideration for ASD heterogeneity

Crash Course in Immunology

- **Innate** immune system
 - Barriers
 - Cells: Granulocytes (a white blood cell)
 - Molecules: Pattern recognition and Toll-like receptors
- **Properties:**
 - Recognizes common threat patterns
 - Fixed, hardwired, no learning

Crash Course in Immunology

- **Adaptive** immune system
 - Organs: Thymus, Lymph nodes, Bone marrow
 - Cells: Lymphocytes (another white cell)
 - Molecules: Immunoglobulins (antibodies)
- **Properties**
 - Context-specific
 - Capable of learning
 - Memory

Crash Course in Immunology

- Common to both systems
 - Cytokines
 - Communication between cells
 - Intensity, character, duration of response
 - Complement
 - Destruction of targets
 - Upregulated in inflammation

Altered Cytokine Profiles

- ASD has increased pro-inflammatory (Th1) and dampened anti-inflammatory (TH2) response
- Transforming growth factor-Beta (TGF-B)
 - Decreased blood levels in ASD adults
 - Increased brain levels post-mortem
- Macrophage Inhibitory Factor (MIF)
 - Brain: pro-inflammatory, neuro-endocrine
 - Higher plasma levels in ASD, severe behavior

Leptin

- Weight control hormone
- Produced by fat cells and white cells
- Shares functional similarities w/ IL-6, a pro-inflammatory cytokine facilitating communication bet. CNS and immune sys.
- Crosses blood brain barrier
- Elevated in autism, esp. early-onset vs. clinical regression

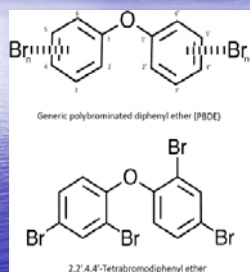
Immunoglobulins

- Proteins produced by B lymphocytes
- Target entities for destruction and removal
- Several classes, each with a specific role
- Decreased levels total IgG, IgM in ASD, lowest levels w/ most severe behavior
- Elevated levels of IgG4 (link to disease?)
- Significance unclear: shared pathway?

Altered Cellular Immunity

- Natural Killer (NK) cells
 - Viruses, pregnancy, tumors, autoimmunity
 - Increased expression of receptor and effector molecules, but diminished activity
- Monocytes
 - Innate: ID pathogens and direct response
 - ASD monocytes respond differently to stimulation of their Toll-like receptors (TLR)

Polybrominated Diphenyl Ethers Environmental Toxins: PBDEs



Altered Sensitivity to Environmental Toxins

- Ashwood et, al. 2009 PBMC from ASD vs control pretreated w/ PBDE then LPS stim
- PBDE suppressed production of pro-inflammatory cytokines in controls
- In ASD cells, PBDE treatment INCREASED production of pro-inflammatory cytokines
- Different sensitivity to environmental toxins? Altered immune regulation?

Allergy and ASD?

- Early studies lacked appropriate control groups.
- Better studies have shown no difference:
 - Frequency of allergic d/o
 - Number of positive skin prick tests
 - Serum IgE levels

Autoimmunity

- When the immune system targets the body's own tissues.
- Often leads to disease BUT...
- A certain amount of autoimmunity (self-reactivity) is **normal** and **necessary** for proper immune function
 - Turning off inflammation, limiting damage
 - Disposing of damaged, rogue cells (cancer)
 - Education of immune cells in thymus

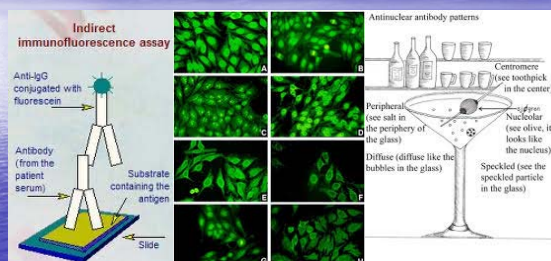
Antibodies to Neural Antigens

- Circulating antibodies directed against brain proteins in ASD
- Higher rate of plasma IgG against golgi cells in ASD
- significance unknown
- Also found occasionally in neurotypic and developmental delay without ASD





Anti-Nuclear Antibodies (ANA)

- Antibodies directed against protein and/or nucleic acid components of the cell nucleus
- Associated with lupus and many other autoimmune diseases but also found in healthy people
- Children with autism have a higher frequency of ANA (20% vs. 2.5%)

What is an ANA?



Different ANA patterns correlate with different diseases

Medscape www.medscape.com			
Peripheral (rim)		anti-DNA (not seen on HEp-2)	SLE
Homogeneous (diffuse)		anti-DNA anti-histone anti-DNP (nucleosomes)	RA & SLE Misc. Disorders (anti-ssDNA)
Speckled		anti-Sm & RNP anti-Ro & La anti-Jo-1 & Mi-2 anti-Scl-70	SLE & SS PM/DM PSS (Systemic)
Centromere		anti-centromere	PSS (CREST)
Nucleolar		anti-nucleolar	SLE & PSS

What is lupus?

- This is lupus.



What is lupus?

- This is also lupus.



Behavior and Autoimmunity Precedents

- Neuropsychiatric SLE (lupus) antibodies
 - React to NMDA receptor for glutamate
- Autoantibodies to specific nervous system components also reported in:
 - Schizophrenia
 - Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS)
 - Gilles de la Tourette's Syndrome

And what would a talk by an NIH graduate be without...

Mouse Models



BTBR Mouse

(Be The Better Rodent)

- Exhibits core features of autism:
 - Reduced sociability
 - Spend less time sniffing
 - Impaired social communication
 - Fewer scent marking behaviors
 - Increased repetitive/compulsive behaviors
 - Excessive self-grooming, but not the usual way
 - Compulsive marble burying

BTBR model

- Increased expression of pro-inflammatory cytokines IL-1B, IL-6, IL-12 in brain tissue w/ increased microglia #s/activation
- Increased IL- 33 in brain correlated w/ increased impairment in behavior.
- Skewing in macrophage/microglia subtype toward M1, favoring IL-12 production over IL-10 (pro-inflammatory response)

MIA Mouse

(Maternal Immune Activation)

- The ONLY environmental mouse model of ASD with all three core impairments
- Activated by exposure to IL-6, poly(I:C), LPS, or influenza with similar results
- MIA offspring exhibit prepulse inhibition, stereotypic behavior, decreased social preference

MIA Mouse

- Dysregulated immune function
 - Systemic deficits in T-regs de-suppress both innate and adaptive immune responses, causing pro-inflammatory milieu
 - Increased IL-6 by Th cells (pro-inflammatory)
- Could ASD-related behavioral abnormalities be corrected by repairing immune function?

Treatments for ASD

Based on inflammation and autoimmune dysfunction

- Intravenous immunoglobulin (IVIG)
- Helminth-based treatments
- Hyperthermia-based treatments
- Minocycline
- Probiotics
- Stem Cell Therapies

I hope I met your expectations

- Thank you.



Acknowledgement

- P. Goines and J. Van der Water, The Immune System's Role in the Biology of Autism, Curr. Opin. Neurol. 2010 April; 23(2): 111-117.
- This is an NIH Public Access Author Manuscript.
