

Slide
1




CNNH
The Center for Neurological and Neurodevelopmental Health®

and the
NeurAbilities Clinical Research Center of New Jersey
Gibbsboro, New Jersey, USA

**“Tourette Syndrome and Autism:
Similarities and Differences”**


**New Jersey Center for
Tourette Syndrome and Associated Disorders**
May 13, 2015
Mark Mintz, M.D.

Slide
2



Disclosures

- I have no financial relationships that are directly related to the course content of this lecture.
- Other financial and other relationships that might be perceived as a potential conflict requiring disclosure include the following:
 - Dr. Mintz is President, CEO, Founder of The Center for Neurological and Neurodevelopmental Health, LLC, (CNNH) and Clinical Research Center of New Jersey, LLC, (CRCNJ), and President of NeurAbilities.
 - In the past 12 months, Dr. Mintz has functioned as Principal Investigator for research contracted through the Clinical Research Center of New Jersey, LLC, (CRCNJ) sponsored by the following companies: Sunovion, Pfizer, Eisai, Inc, Allergan. CRCNJ receives funding to conduct the clinical trial.
 - Dr. Mintz is the principle investigator for research funded by the State of New Jersey, through the Governor’s Council for Medical Research and Treatment of Autism.
 - CNNH is a customer and end-user of Electrical Geodesics, Inc. (EGI), but CNNH has not received financial compensation from EGI. CNNH is a customer of Courtagen Life Sciences and has published research with some of their scientists as co-authors, but CNNH has not received financial compensation from Courtagen Life Sciences.
 - Dr. Mintz is Medical Director for Autism Services Group, contracted through CNNH. CNNH receives a stipend for this service.

 ©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
3




The Center for Neurological and Neurodevelopmental Health (CNNH)

- Founded in 2005 by Mark Mintz, M.D.
- CNNH provides a comprehensive array of assessment, treatment and support services for those affected by Neurodevelopmental Disabilities, Neurobehavioral/Neuropsychiatric Disorders, Brain Injury and other Neurological and Neuropsychological Disorders: unique “Specialty Care Medical Home®” health care delivery system.
 - The Clinical Research Center of New Jersey (CRCNJ), simultaneously founded in 2005, provides access to clinical trials and investigator-initiated research studies.
 -  **NeurAbilities** an independent 501(c)(3) public charity established in 2008, dedicated to providing access to the most effective and comprehensive diagnostic, treatment and innovative services available. www.neurabilities.org
- Services are provided in office, school, home and community environments.
- 50+ Professional/Support Staff
- Over 30,000 ft² of state-of-the-art facilities in:
 - Voorhees, NJ
 - King of Prussia, PA
 - Rutherford, NJ
 - Wall Township, NJ




 ©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
4




Tourette Syndrome (TS) and Autism Spectrum Disorder (ASD)

- TS and ASD are defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5
 - American Psychiatric Association
- Diagnostic paradigms are based on behavioral and developmental symptoms and signs
 - Diagnoses are not dependent upon biological causes
 - Many International Classification of Diseases (ICD)-9 correlates and co-morbidities
- Creates biologically heterogeneous groups with neurodiversity
- Creates dilemma of co-occurring conditions arising by chance
 - Need to develop diagnostic paradigms that are the final common pathway of common biological substrates.

 **CNNH**
The Center for Neurobiological and Neurodevelopmental Health

©2005 - 2014 CNNH. All rights reserved. www.CNNH.org


Slide
5



TS and ASD


Neurobiological Symptoms and Signs

- Central Nervous System
 - Motor system: coordination, planning, tone
 - Cerebellar functioning
 - Motor stereotypies, involuntary movements, tics
 - Aberrations of head growth velocities
 - Neurodevelopmental delays
- Neuropathological changes
- Neuroradiological findings
- Molecular/Genetic Substrates
- Neuropsychological/Neurocognitive Disorders
- Learning Disorders
- Neurological Co-Morbidities
 - Epilepsy, Sleep Disorders, Other
 - Autonomic Nervous System Dysregulation
 - "autonomic over-responsivity"
- Medical Co-Morbidities
 - Gastrointestinal, Immunological, Other
- Neuropsychiatric Syndromes
 - ADHD
 - Obsessive Compulsive Disorder
 - Anxiety Disorders
 - Mood Disorders

 **CNNH**
The Center for Neurobiological and Neurodevelopmental Health

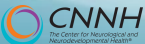
©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
6



Diagnostic Dilemmas: DSM-5 Pitfalls

- Ubiquitous and General Criteria
 - Nonspecific
 - Qualitative
 - Subjective
- Ignores Neurobiological Etiologies
 - Diagnosis not dependent upon biological cause
- Leads to Heterogenous Groups/Cohorts
 - Neurobiologically Diverse
 - Poor Phenotypic Differentiation
 - Leads to Flawed Research and Wasted Dollars
 - Poorly Targeted Therapies
 - Missed Opportunities: Disease Modification, Prevention, Cure
- Need to move to "biological phenotyping" and "clinical profiling"
- "...neurobiological studies will be useful for determining...whether the DSM-5 ASD diagnosis can be empirically parsed into biologically meaningful subphenotypes..." [Frazier et al. 2012]

 **CNNH**
The Center for Neurobiological and Neurodevelopmental Health

©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
7


 Autism Spectrum Disorder

- Behaviorally and Developmentally Defined Diagnosis
 - Behavioral/clinical symptoms and signs are ubiquitous, non-specific and subjective
- Neurobiological Disorder of Early Brain Development
 - Diagnosis is not dependent upon etiology
 - Final common pathway
 - Overlaps other disorders and normality
 - Multiple mechanisms and biological etiologies
 - Not a "mental health" disorder




 ©2005 - 2014 CNNH. All rights reserved. www.CNNH.org


Slide
8

 ASD Epidemiology


- National Prevalence 1:88 (eight years old)
 - New Jersey 1:49 (2%)
- Male:Female; 4:1 to 8:1
- Sibling incidence 1:15
- Similar rates across cultures
 - Global rate 62/10,000 (0.62%)
- Twin and sibling concordance
- Increased risk with advanced maternal or paternal age?




Elisabagh M et al. Global prevalence of autism and other pervasive developmental disorders. Autism Research 2012; 5: 160-170.
Monitoring (ADDM) Network, Centers for Disease Control, www.cdc.gov
Durkin et al. Advanced parental age and the risk of autism spectrum disorder; Am J Epidemiol 2008.

 ©2005 - 2014 CNNH. All rights reserved. www.CNNH.org


Slide
9

 DSM-5

- Autism Spectrum Disorder
 - Two-factor (dyad) dimensional diagnostic paradigm:
 - Social Communication domain
 - Restricted Interests/Repetitive Behaviors domain
 - "lumping" versus "splitting" (single diagnosis)
 - "Loss" of Asperger Disorder diagnosis: threatens loss of services
 - Improved diagnostic specificity compared to DSM-IV
 - May include sensory hypo-/hyper-responsivity
 - Lacks phenotypic and etiological dimensions
 - May change epidemiology unless "relaxation" of criteria
 - Studies using DSM-IV may not be comparable to those using DSM-5
 - Specificity at the expense of Sensitivity
- "...neurobiological studies will be useful for determining...whether the DSM-5 ASD diagnosis can be empirically parsed into biologically meaningful subphenotypes..." [Frazier et al. 2012]


 ©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
10




Biological Causes of Autism

- Assess for Mimickers of Autism
 - Hearing Loss
 - Cognitive Deficiency
 - Developmental Language Disorders
- Neurobiological syndrome
 - Neurological disorder of brain development and organization ("connectivity" or disorder of synaptogenesis)
 - Association of Intellectual Disabilities
 - Association of Epilepsies
 - Neurogenetic surrogate markers
 - 20-30%+ and growing
 - Possible environmental influences or triggers
- Subset of associations with Neurometabolic and Neurotransmitter Disorders
 - "Energy" disorders: mitochondrial disorders/dysfunction and channelopathies
 - Exacerbation by inflammation
- Congenital cerebral developmental or acquired brain abnormalities
 - Fetal Infections; Intrauterine Toxic Exposures; Prematurity
- Other controversial etiologies: Neurotoxins, Autoimmune, Gastrointestinal, Infectious/Viral and more
- "Idiopathic": suspected but unknown neurobiological etiology
 - Are Co-Morbidities/Co-Occurring Conditions:
 - Coincident?
 - Contributory?
 - Causative?


 ©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
11




Tourette Syndrome/Disorder DSM-5

- Presence of multiple motor tics AND vocal tics
- Tics for at least one year ("chronic")
 - Tics can be "off/on"
 - Timed from the point of the first tics
- Tics prior to 18 years of age
- Symptoms and signs are not the result of medication or other drugs, or due to other medical conditions
- Related DSM-5 diagnoses:
 - Provisional Tic Disorder
 - Less than one year duration
 - Chronic Motor or Vocal Tic Disorder (CTD)
 - Tic Disorder Not Elsewhere Specified (TDNES)
 - Stereotypic Movement Disorder


 ©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
12



Epidemiology of TS

- Parent Report (CDC Telephone Survey)
 - 3 cases per 1,000 children = 148,000 children
 - Additional numbers with various Tic Disorders
 - Many adults afflicted
 - 79% with co-morbid disorders
 - 60% with additional diagnosis of ADHD and/or disruptive behavior disorder
 - However, the reverse is not true: the majority of children with ADHD do not have tics or TS
 - 30-40% with co-occurring anxiety and mood disorders
 - 20% diagnosed with Autism Spectrum Disorder

 ©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
13




TS: Associated Neurological & Neuropsychiatric Disorders

- 50-90%
 - Attention Deficit Hyperactivity Disorder (ADHD)
 - Obsessive Compulsive Disorder
 - Other:
 - Anxiety
 - Depression
 - Personality disorders
 - Learning disability
 - Executive dysfunction
 - Impulse Control Disorder
 - Anger management
 - Rage
 - Sleep Disorders
- Mimickers:
 - Seizures
 - Other Movement Disorders
 - Chorea
 - Dystonia, Spasms
 - Benign motor stereotypies
 - Psychogenic Movement Disorders
 - Conversion Disorders
 - Somatoform Disorders
 - Dissociative Disorders
 - Allergies
 - Sleep Movement Phenomena
 - Movement Disorders resolve with sleep

 ©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
14




Co-Occurring TS and ASD

- 22% of ASD patients present with tics (N = 105)
 - 11% chronic motor tics
 - 11% TS
 - 59% with family history of tics


Canitano and Vivanti, Autism 2007

- TS International Database Consortium Registry
 - 5% with TS had comorbid ASD
 - 13-fold increased risk of ASD from TS
 - Multiple additional co-morbidities when co-occurring disorders, particularly neurobehavioral disorders

Burd et al., J Child Neurol 2009


 ©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
15




Tics, TS and ASD

- Convergence of biological, environmental and social constructs
 - Brain
 - Mind
 - Genetics
 - Neurometabolic/Neurochemistry
 - Anatomic: brain circuits
 - Behavior
 - Social development
- Similarities
 - Phenomenological
 - Obsessions, compulsive behaviors, involuntary movements, poor speech control or impaired communication, echolalia, socialization deficits
 - Epidemiological
 - Diagnosable in childhood
 - Affects males more than females
 - Pathogenic
 - Neuroradiological and pathological evidence of "connectivity" and "synaptic" aberrations
 - Genetic
 - Common and overlapping susceptibility genes


 ©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
16




Shared Clinical Features and Commonalities

- Speech/Language
 - Echolalia, Palilalia
 - Coprolalia in TS, not ASD
 - Perseverations
- Neuropsychiatric Disorders and Symptoms
 - Obsessive Compulsive Disorder (OCD) and behaviors
 - ADHD
 - Self-injurious Behaviors (SIB)
- Neuropsychological Findings
 - Learning Disorders
 - Intellectual Disabilities
 - Social Deficits
- Motor Signs
 - Repetitive Movements
 - Tics occur at higher prevalence in TS than ASD
 - Motor stereotypies and repetitive behaviors common in ASD

 **CNNH**
The Center for Neurological and Neurodevelopmental Health


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
17




Repetitive Movements

- Akathisia
 - Internal sensation of restlessness leading to repetitive movements such as pacing
 - Not stereotyped and patterned
- Tics
 - Non-rhythmic and discrete
 - Change in location and type over time
 - Wax and wane in frequency and severity

 **CNNH**
The Center for Neurological and Neurodevelopmental Health


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
18



Motor and Vocal Tics

- Sudden, rapid, recurrent, non-rhythmic movements or sounds
- Simple Tics involve one group of muscles
 - Rapid: Blinking, shrugging, head jerk, throat clearing, grunting, "sounds/noises" and more
 - Dystonic/tonic: such as shoulder rotation, blepharospasm
- Complex Tics involve several muscles, coordinated movements
 - Bending, gyrate, echolalia, palilalia, coprolalia
- Premonitory sensations

 **CNNH**
The Center for Neurological and Neurodevelopmental Health

©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
19




Repetitive Behaviors in ASD

- Major Types
 - Self-Injury
 - Compulsions
 - Rituals
 - Sameness
 - Restrictions
- Repetitive Movements
 - Stereotypies
 - Other types include tics, akathisia
- Stereotypies
 - "Self-Stimulation" or "Stimming"
 - Gratification Behaviors; Infantile Masturbation (dyskinesia?)
 - Rhythmic, patterned, repetitive, purposeless, involuntary
 - Body Rocking, Head Nodding, Hand/Arm Flap, Walk in Circles, Finger Flicking, Facial Grimacing
 - Rhythmic and Continual
 - Little change over time
 - Can resolve or persist into adulthood
 - Treatment:
 - Behavioral
 - Possibly medication but data is scant

 **CNNH**
The Center for Neurological and Neurodevelopmental Health


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
20




Stereotypies vs Tics

Stereotypies	Tics
<ul style="list-style-type: none">• Present < 4 years old• Consistent, fixed• Arms, hands, entire body• Rhythmic and prolonged• No premonitory urges• Precipitated by stress, anxiety, excitement, fatigue, engagement, anticipation• Quickly stop/cease with distraction or awareness• Familial tendencies• Less responsive to alpha-agonists and neuroleptics	<ul style="list-style-type: none">• Present 5-7 years old• Evolve over time• Eyes, face, head, shoulders• Brief and intermittent• Premonitory Urges• Precipitated by stress, anxiety, excitement, illness, lack of sleep/fatigue• Can suppress briefly and voluntarily: behavioral techniques• Familial tendencies• Respond to alpha-agonists and neuroleptics

 **CNNH**
The Center for Neurological and Neurodevelopmental Health

©2005 - 2014 CNNH. All rights reserved. www.CNNH.org


Slide
21



TS and ASD


Biological Commonalities and Differences

- Familial/Genetic
- Anatomical/Connectivity
 - TS involves the prefrontal cortex and basal ganglia
 - Cortico-striatal-thalamo-cortical (CSTC) circuits
 - Integrates movement, sensation, emotion and attention
 - MR/DTI data suggest possible enhanced pathways
 - TS may have volumetric changes of the basal ganglia, thalamus, corpus callosum, and cortex
- Psychopharmacology
 - Dopaminergic
 - Adrenergic
 - Serotonergic
- Associated Neuropsychiatric Syndromes
 - Attention Deficit Hyperactivity Disorder (ADHD)
 - Obsessive Compulsive Disorder
 - Anxiety Disorders
- Autoimmune mechanisms
- "Acquired" forms; "Neurodevelopmental" forms

 **CNNH**
The Center for Neurological and Neurodevelopmental Health

©2005 - 2014 CNNH. All rights reserved. www.CNNH.org


Slide
22



Genetic Overlaps


- No common dominant gene mutations of large effect
- Polygenic is the norm rather than exception
 - Gene variations represent risk and susceptibility
- May be environmental triggers
- TS and ASD have similar gene variations affecting brain anatomy, neuronal circuitry and synaptic signaling: brain “connectivity”

Clarke et al. Translational Psychiatry, 2012.

 **CNNH**
The Center for Neurogenetics and Neurodevelopmental Health


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
23




Genetics and Tourette Syndrome

- Familial inheritance patterns
 - “Linkage” studies
 - Some findings, but not generalizable: may be isolated to singular families
- Pharmacological responses suggest dopaminergic, serotonergic, or adrenergic pathways are involved
 - Many candidate genes assessed affecting these pathways
 - No dominant gene with large effect discovered
- Possible primary molecular defect may cause downstream neurochemical changes in neurotransmitter balance
 - Serotonin
 - Dopamine
 - Glutamate




IT'S HARD TO BELIEVE, BUT HE'S FATHERED THREE HYPERACTIVE CHILDREN.

© 2005 - 2014 CNNH. All rights reserved. www.CNNH.org

 **CNNH**
The Center for Neurogenetics and Neurodevelopmental Health


Slide
24



TS and ASD Genetic Overlaps


- Rare but large Copy Number Variants (CNV)
 - CNV up to 52 megabases spanning 447 genes
 - Histaminergic signaling pathways
 - Has an immunological role
 - Chemical messenger in brain and gut
 - Gamma-aminobutyric acid (GABA) mechanisms
 - GABA dampens brain signals
- TS individuals twice as likely to have CNVs disrupting genes associated with ASD
 - Not identified in intellectual disability or schizophrenia
 - CNTNAP2, DISC1, AUTS2, 16p11.2, 22q11.21 genomic regions

Fernandez et al. Biological Psychiatry 2012.

 **CNNH**
The Center for Neurogenetics and Neurodevelopmental Health

©2005 - 2014 CNNH. All rights reserved. www.CNNH.org


Slide
25




Targeted Exome Sequencing *Mitochondrial Disorders and Channelopathies*

- N = 24 with Generalized Anxiety Disorder or OCD
 - All with "autonomic over-responsivity" (AOR)
 - Diaphoresis, tremulousness, akathisia, emesis, flushing, palpitations/tachycardia, migraine phenomena, sleep dysregulation
 - 38% with gene variations rated as "pathogenic" or "likely pathogenic"
 - 83% with gene "variants of uncertain significance"
 - 87% with at least one gene variant rated as "pathogenic", "likely pathogenic", or "variant of uncertain significance"
 - All variants "actionable"
 - Potential treatment intervention (medication or specific metabolic/enzymatic supplement or dietary option)
 - Triggering additional diagnostic investigations/testing
 - Presumed biological cause or contributor to the patients phenotype
 - Alerting to potential cardiac arrhythmia or malignant hyperthermia susceptibilities
 - Alerting to avoidance of certain medications
 - Conclusion: AOR often related to channelopathy, particularly of calcium and potassium

Mintz et al. 2014
www.CNNH.org

 ©2005 - 2014 CNNH. All rights reserved.


Slide
26




Does PANDAS Exist?

- Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections
- Acute Onset of:
 - Obsessive Compulsive Disorder (OCD)
 - Tic Disorder/Tourette Disorder
 - Antecedent streptococcal infection
 - Reminiscent of Rheumatic Fever (RF)
- Described in early 1990s
 - No unique strain of Group A beta-hemolytic streptococcal (GABHS) infection identified
 - Reports of antibodies to caudate nucleus, but also controls
 - Reports of B-lymphocytes with D8/17 epitope: similar to RF with Sydenham's Chorea

www.CNNH.org

 ©2005 - 2014 CNNH. All rights reserved.


Slide
27




Does PANDAS Exist?

- Clinical Criteria:
 - Presence of OCD, Tic Disorder (chronic), or both
 - Onset between three years and puberty (3-12 y/o)
 - Episodic course with abrupt onset or dramatic exacerbation of symptoms
 - Recurrence, remissions, exacerbations
 - Symptom exacerbations temporally related to GABHS infection
 - Throat culture
 - Many types of organisms can cause pharyngitis
 - Elevated antistreptococcal antibody titers
 - Serial titers: elevation
 - Can have slow rate of decline
 - Usually no evidence of rheumatic carditis
 - Associated Neurological Findings:
 - Choreiform movements
 - Tics
 - Hyperactivity
 - Others

www.CNNH.org


 ©2005 - 2014 CNNH. All rights reserved.

Slide
28




Does PANDAS Exist?

- Psychiatric Co-Morbidities
 - Emotional lability
 - Separation anxiety
 - Night-time fears
 - Oppositional behaviors
 - Deterioration in school performance
- Relapsing/Remitting pattern
 - Dramatic and explosive exacerbations
 - Temporally linked to evidence of GABHS
 - Interspersed periods of relative quiet

 **CNNH**
The Center for Neurological and Neurodevelopmental Health®


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
29




Does PANDAS Exist?

- 20% of grade school children are chronic carriers of GABHS
- Symptoms have a long latency from infection in many reported cases (compare RF)
- Many cases have pre-existing tics disorders or neuropsychiatric conditions:
 - Cause versus exacerbation of underlying predisposition
- Anti-neuronal antibodies elevated in those diagnosed with PANDAS, but also many controls
- Presentation consistent with other mechanisms:
 - Encephalitis
 - Vasculitis
- No subsequent rheumatic complications reported
 - Possible single rheumatic manifestation (compare post-strep reactive arthritis)

 **CNNH**
The Center for Neurological and Neurodevelopmental Health®


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
30




PANDAS – Treatments

- Treatments
 - Antibiotics for GABHS infection
 - Studies of long-term or prophylactic antibiotics not supportive
 - Contradistinction to Rheumatic Fever
 - Why use antibiotics for an autoimmune disorder?
 - Destroy the antigen (bacteria) causing the immunological cascade
 - Direct immunologic-modifying properties of some antibiotics
 - Intravenous Immunoglobulin (IVIG), Steroids
 - Studies not supportive
 - Plasma exchange
 - Studies not supportive
 - Tonsillectomy for recurrent GABHS infection
 - SSRI, other medications for neuropsychiatric complications
 - Behavioral therapies

 **CNNH**
The Center for Neurological and Neurodevelopmental Health®


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
31

 **Childhood/Pediatric
Acute Neuropsychiatric Syndrome
(CANS/PANS)**


- CANS/PANS: Broadening of the "PANDAS" diagnosis
 - Includes PANDAS
 - Questions the PANDAS diagnosis as unique
 - Inconclusive and conflicting scientific support
 - Tics (20-30%) and OCD are common in childhood
 - Requires dramatic onset of neuropsychiatric symptom(s)
 - No specific organism, age range, or recurrence of symptoms needed
 - Tics not necessary
 - Choreiform "piano playing" movements raise issue of SC/RF
- Emphasis on history, examination, differential diagnosis, laboratory testing
- Appropriate therapies
 - Targeted to specific etiology or symptom

Singer et al., Journal of Pediatrics, 2012


 **CNNH**
The Center for Neurological and
Developmental Health


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
32

 **Epilepsy Defined**


- A tendency toward recurrent seizures unprovoked by any systemic or acute neurologic insults
- **Seizure:** the clinical manifestation of an abnormal and excessive synchronization of a population of cortical neurons
 - Hughlings Jackson: "occasional, excessive, and disorderly discharge of gray matter"
 - Diversity of Causes: Epilepsy is the final common pathway of various biological mechanisms and triggers
 - The "Epilepsy Spectrum" disorders




 **CNNH**
The Center for Neurological and
Developmental Health

©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
33


 **Epilepsy and Epileptogenesis: Overlap with
Neurodevelopmental Disorders**

- Symptomatic
 - Acquired structural lesions
 - Stroke
 - Infections
 - Brain Injury/Trauma
 - Mesial Temporal Sclerosis
 - Tumors
 - Developmental
 - Cortical Dysplasia
 - Neurometabolic Disorders
 - Prolonged/recurrent seizures
- Idiopathic/Cryptogenic
 - Genetic
 - Neuronal Migration Disorders
 - Neurogenetic Disorders
 - Tuberous Sclerosis
 - Gene-Environmental interactions
 - Channelopathies
 - Connectivity
 - Synapsopathies
 - Axonal Sprouting
 - Dendritic Disorganization
 - Common neuropathological and genetic substrates may provide clues for etiologies and treatments

 **CNNH**
The Center for Neurological and
Developmental Health


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
34




Epilepsy-Autism Connection

- Prevalence
 - 6% to 26% in children and adolescents [Amiet et al. 2008, McVicar et al. 2005; Suren et al. 2012]
 - Higher risk with concomitant Cerebral Palsy or Intellectual Disability
 - Cumulative risk in adults as high as 67%
 - High percentage of "subclinical spikes" and other EEG abnormalities
- Epilepsy and Neurodevelopmental Disorders
 - Common association
 - Causes of neurodevelopmental disorders can overlap with causes of epilepsy
 - Common neuropathological and genetic substrates may provide clues for etiologies and treatments
 - Epilepsy increases risk of mortality in autism [Pickett et al. 2011]
 - Epilepsy associated with language regression




©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
35




Epilepsy and Tourette Syndrome

- Not a common association
 - History of Febrile Convulsions may increase the risk of developing TS (Tu et al. 2014)
 - Possible case of Sudden Unexpected Death in Epilepsy (SUDEP) and Tourette (Doherty and Sloan, 2010)
 - Scattered reports of electroencephalographic abnormalities in TS or co-morbid conditions (Bergen et al. 1982; Barabas et al., 1984; Verma et al., 1986; Rizzo et al. 2010; Wannag et al., 2010; Neville et al., 2001; Semerci, 2000; Hyde et al., 1994)
 - Also reports of no EEG differences compared to non-TS (Neufeld et al., 1990; Krumholz et al., 1983)
- Tics can be mistaken for myoclonic epilepsy or focal seizures




©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
36



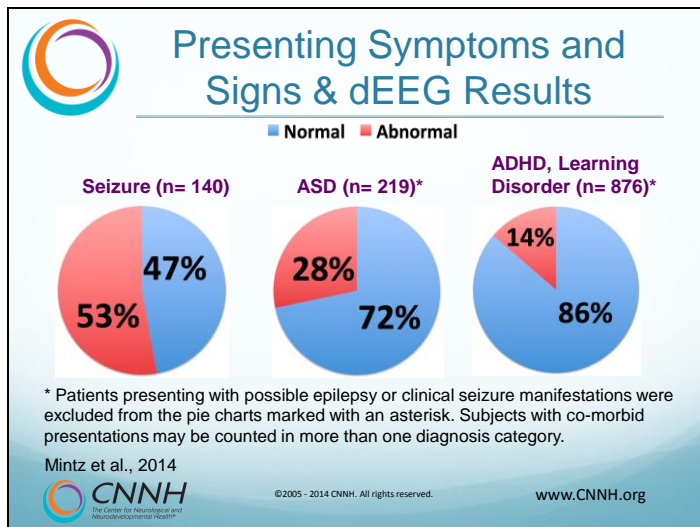
Subclinical Spikes

- **"Subclinical Spikes" (SCS)** are electrographic spikes without known or observable clinical seizure manifestations, and may be associated with neuropsychological, behavioral, and academic impairments (Mintz et al. 2009).
- Studies have shown SCS to be associated with momentary decrement and/or chronic changes in cognitive function (Kleen et al. 2013; Mintz et al. 2009). Other studies have associated electroencephalographic (EEG) abnormalities with non-epileptic conditions (Ogrim et al. 2014; Peters et al. 2013; Loo and Makeig 2012; Brown et al. 2012; Tye et al. 2011).
- We hypothesize that patients presenting with neurological disorders but without epilepsy can have clinically significant "unexpected" EEG abnormalities including SCS.

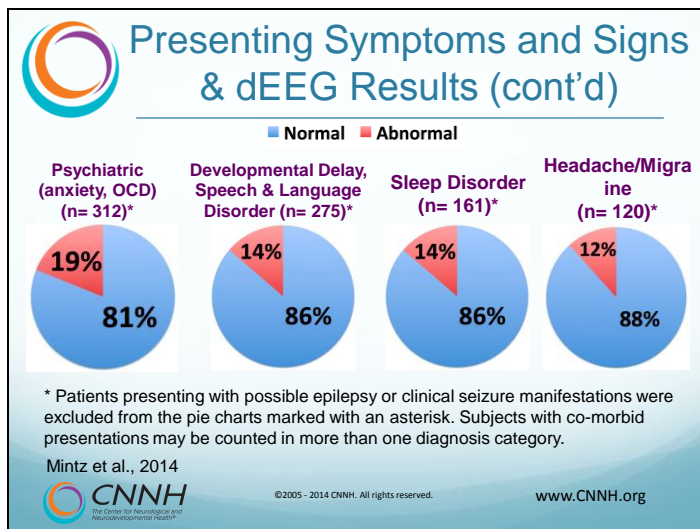


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

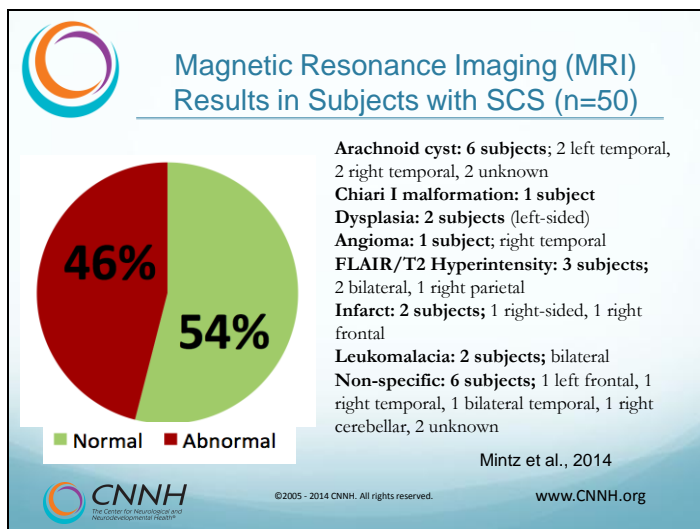
Slide
37




Slide
38



Slide
39




Slide
40




Conclusions

- Unexpected, significant EEG abnormalities should be suspected in patients with neurological, neurodevelopmental, and neuropsychological disorders with non-epilepsy presentations.
- Comprehensive evaluations that incorporate neurophysiological and neuropsychological testing can inform patient management.
- Suppression of SCS has been associated with neuropsychological and behavioral improvements [Mintz et al., 2009].
- Epilepsy may represent a “spectrum” disorder including those with cortical electrical abnormalities without observable seizures or prodromal to observable seizures, but with disturbance of brain function.
- EEG is an important neuroimaging tool that is a direct, real-time measurement of neuronal function.

 **CNNH**
The Center for Neurological and Neurodevelopmental Health


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
41




TS and ASD Neurodiagnostic Overlaps

- Hearing and Vision
- Neurology/Neuropsychiatry
- Neuropsychology
 - Psychoeducational/Learning Disorders
 - Cognitive Levels
 - Social Development/Communication
- Functional Behavioral Analysis
- Neurophysiology
 - Dense Array EEG (dEEG)
 - Dense Array Event Related Potentials (dERP)
- Neuroimaging
- Molecular/Genetic
 - Chromosomal Microarray Analysis (CMA)
 - Targeted Exome DNA Sequencing
 - Whole Exome Sequencing
 - Other Molecular Analyses
 - Trinucleotide Repeats/Expansions
 - Disease specific
- Biochemical Profiles
 - Electrolytes/Elemental/Ions
 - Biochemical/Enzyme Assays
- Metabolic Studies
 - Disorders of Cellular Energy Metabolism
 - Other Neurometabolic Disorders
- Endocrine
 - Hypothalamic-Pituitary-Thyroid-Adrenal Axis
- Sleep Evaluation
- Gastrointestinal/Nutritional
- Infectious/Immunologic/Inflammatory
 - Allergies
 - Autoimmunity
 - Microbial
- Cerebrospinal Fluid
 - Neurotransmitter disorders
 - Neurometabolic disorders
 - Latent or Chronic Brain Infections
 - Brain Inflammation

 **CNNH**
The Center for Neurological and Neurodevelopmental Health

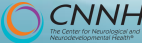
©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
42




Tourette Disorder Therapies and Treatments

- Education and Demystification
 - Patient and Peers
- Health/Lifestyle Optimization
 - Adequate Sleep; Reduce Stress; Healthy Diet; Sufficient Exercise
 - Target causes and mimickers
- Behavioral
 - Comprehensive Behavioral Intervention for Tics (CBIT)
 - Cognitive Behavior Therapy (CBT)
 - Habit Reversal Training (HRT)
 - Exposure-Response Therapy
- Pharmacological
- Brain Stimulation (neuromodulation)
 - Deep Brain Stimulation (DBS)
 - Transcranial Magnetic Stimulation (TMS)
 - Transcranial Direct Current Stimulation (tDCS): anecdotal
- Neurosurgical: disruption of brain networks
 - Variable results; not well studied; not recommended

 **CNNH**
The Center for Neurological and Neurodevelopmental Health


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
43




ASD Therapies and Treatments

- Treatments are targeted to the clinical/biological profile
 - Target mimickers and/or biological causes/contributors
 - Core Symptoms/Signs
 - Target co-morbid disorders
- Non-pharmacological interventions are optimized
 - Behavioral
 - Educational
 - Speech/Language and other collaborative therapies
 - Social Developmental
 - Creative Arts and many others
- Pharmacological Therapies are adjunctive
 - Facilitate non-pharmacological therapies
 - Target co-morbid disorders, mimickers, and causes/contributors
 - Promising research for targeting core symptoms

 **CNNH**
The Center for Neurological and Neurodevelopmental Health


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
44




TS and ASD Pharmacological Overlaps

- Medications for core symptoms/signs and co-morbidities
 - Alpha-Adrenergic Agonists
 - Stimulants and Non-Stimulants (SNRI)
 - Serotonergic Drugs (SSRI)
 - Anti-Epileptic Drugs
 - Benzodiazepines
 - Beta-blockers
 - Sleep Medications
 - NMDA (Glutamate) Antagonists
- Genetics may inform therapies
 - Pharmacogenomics
 - Targeted Exome DNA Sequencing
- Immunological Therapies
 - Steroids
 - Intravenous Immunoglobulin
- Antimicrobial Therapies

 **CNNH**
The Center for Neurological and Neurodevelopmental Health


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
45




TS and ASD Other Treatment Overlaps

- Behavioral Therapies
 - Applied Behavior Analysis
 - Comprehensive Behavior Interventions for Tics
 - Cognitive Behavior Therapy
- Creative Arts Therapies
- Sleep Hygiene
- Dietary Approaches
- "Mitochondrial Cocktails", anti-oxidants, and micronutrients
- Hormonal replacement or interventions
- Gastrointestinal interventions ("biome")
- Neuropsychological/Neurocognitive interventions
- Educational interventions

 **CNNH**
The Center for Neurological and Neurodevelopmental Health


©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
46



“NATURAL” THERAPIES


- Quality Control
- Purity
- Active Ingredient
- Many Toxins Are “Natural”
- High Doses Can Become Toxic
- “Aura” Of Food Supplements
- Seduction



CNNH
The Center for Neurological and Neurodevelopmental Health®

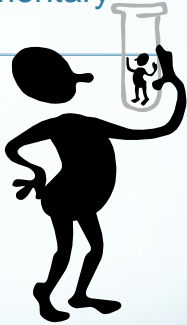
©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
47



Alternative/Complementary Therapies


- CRITERIA FOR USE:
 - SAFETY
 - NO KNOWN TOXICITIES
 - DOSAGE DATA
 - EFFICACY
 - EVIDENCE-BASED
 - Avoid Observational/hypothetical
 - Avoid Testimonials/anecdotes
 - Sustainability and generalization of response
 - SCIENTIFIC SENSE
 - What is the hypothetical, theoretical or scientific basis?
 - COST NOT PROHIBITIVE
 - “a balanced diet is good, but vitamin supplementation is most likely to produce expensive urine”
- Unproven “Fad” Therapies
 - Effective therapies are delayed
 - Deplete/divert financial, research and psychosocial resources
 - If it sounds too good to be true, it probably is!
 - Usually promoted outside scientific circles
 - Internet; Popular, non-peer reviewed books; Support groups
 - Can be dangerous and harmful!
 - Take Data!



CNNH
The Center for Neurological and Neurodevelopmental Health®

©2005 - 2014 CNNH. All rights reserved. www.CNNH.org

Slide
48



Conclusions

- TS and ASD similarities and differences
 - Evolving into “spectrum” disorders
 - When co-occurring, can have exacerbation of symptoms
 - Common biological mechanisms
 - Provide clues to potential treatment targets
 - Explosion of genetic/molecular associations
- TS and ASD neurodiagnostics and therapeutics can overlap
 - Assess for biological causes and mechanisms
 - “Biological Phenotyping” and “Clinical Profiling”
 - Can predict susceptibility and severity of ASDs
 - Can lead to efficient and targeted diagnostic investigations
 - Provides guidance for targeted therapeutic interventions
- TS and ASD are biological disorders
 - Diverse and complex biological causes and contributors
 - Final common behavioral pathways and manifestations
- TS and ASDs need a diagnostic paradigm utilizing a hybrid model of clinical, behavioral and biological surrogate markers and clinical signs rather than solely by ubiquitous behavioral symptoms.

CNNH
The Center for Neurological and Neurodevelopmental Health®

©2005 - 2014 CNNH. All rights reserved. www.CNNH.org



Terms of Use

- The recipient and/or possessor of this electronic file agrees not to present and/or disseminate this material in any lecture, educational, or other format, and will use this electronic file solely for the information and education of the recipient and/or possessor. The recipient and/or possessor will not rename the electronic file, or save as an alternative file format.
- The recipient and/or possessor of this electronic file understands that the intellectual property and all contents of this electronic file, and any print out, reproduction, copy, upload, download, modification, adaptation, publication, broadcast, post, transfer or other form of this electronic file, and/or any derivative works, in whole or in part, are the sole property of The Center for Neurological and Neurodevelopmental Health (CNNH).
- The recipient and/or possessor of this electronic file agrees that this file cannot be copied, distributed, reproduced and/or transmitted by any means, including electronic or other forms of transmission, or creation of a printed document.
- The information contained in this electronic file is solely for educational and general informational purposes, and should not be used or construed as direct medical or clinical assessment and/or treatment for an individual and/or group. Always consult a physician or other qualified health care professional for any assessment, diagnostic, medical, clinical and/or treatment advice, interventions or other assistance.
- This Agreement shall be governed by and interpreted in accordance with the laws of the State of New Jersey, without regard to conflict of laws principles.
- This Agreement does not create any agency, partnership, joint venture, employment, or independent contractor relationship between the CNNH and/or the recipient and/or possessor.
- This Agreement shall be binding upon the recipient and/or possessor, and their successors and assignees. This Agreement is personal to, and may not be assigned or transferred by, the recipient and/or possessor.
- This Agreement shall continue in full force and effect indefinitely.



© 2005 - 2014 CNNH. All rights reserved.

www.CNNH.org
