Autism Spectrum Disorders: Challenges and Opportunities

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Objectives

- Define the core deficits of ASD
- Discuss early screening, assessment tools
- Discuss Evidence Based Treatments including Psychopharmacology
- Identify strategies for supporting the child with an ASD and their family

Autism Spectrum Disorders

- Epidemiology
- Definition
- Clinical features
- Screening and diagnosis
- Behavioral Treatment
- Pharmacology
- Family Support

Epidemiology

- Prevalence 1 in 110 in US, CDC 2010
- Prevalence 1 in 94 in New Jersey
- CDC 2007
- Higher in males [4-5 times higher]
- Recurrence risk 3-15%
- 15-20 times higher
- Only ~10-15% with identified etiology


299.00 Autistic Disorder
299.80 Rett Disorder
299.10 Childhood Disintegrative Disorder
299.80 Asperger's Disorder
299.80 Pervasive Developmental Disorder
Not Otherwise Specified (PDD-NOS)
AUTISTIC SPECTRUM DISORDERS

Autism Spectrum Disorders

Core Deficits

- Socialization
- Communication
- Repetitive/ stereotypic behavior

- Deviant relative to developmental level

Definition of ASD

- Qualitative impairment in socialization
  - nonverbal behaviors, peer relationships, social reciprocity (giving, showing, social smiles, gestures, eye contact)

- Deficits in communication
  - delay/ unusual/ absent spoken language; absent imaginative play

- Repetitive/ stereotypic behavior
  - stereotypy, perseverations, rigidity, routines

What is CADDRE?

- PI-Jennifer Pinto-Martin PhD- Epidemiologist
- Center for Autism and Developmental Disabilities Research and Epidemiology - CDC Funding (2001 - 2010)

Studies

- Screening for Early Detection of Autism
- Prevalence of ASD-Surveillance (1:150, 2007) PA
- Study Exploration of Early Development (SEED)

CADDREs in CDC Network

- Pennsylvania
- Maryland/DE
- California
- Colorado
- North Carolina
- Georgia

Who should be screened?

American Academy of Pediatrics:

- Developmental surveillance at every well-child visit (age 21 years) +
  - Formal screening at 9 months, 18 months, 30 months
  - Formal autism screening at 18 months and 24 months
  - School readiness screening at 4 year old well visit

- Developmental screening using formal, validated tools at 8, 18 & 30 months or whenever concern is expressed
Improving Developmental Screening Practices and Early Identification of Autism in Pennsylvania

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Rett Disorder: Regression at 12-18 months

Rett Disorder: Regression at 30-36 months

Autism
- Classical Autism described by Dr. Leo Kanner in 1943
- At severe range of the spectrum
- Higher co-existence
  - mental retardation
  - genetic or other neurological disorders

Identical Twins: Who has Autistic Spectrum Disorder and who has typical development?

Identical Twins? Who has Autism and who has Asperger Disorder?
Clinical Features

- Cognitive abnormalities
  - Uneven profile, Mental Retardation 30-75%
- Gastrointestinal problems (15-40%)
  - Loose stool
  - Constipation
  - Severe food selectivity
- Sleep Disturbances (40-80%)
  - Insomnia- prolonged sleep latency, early risings
  - Parsomnias-teeth grinding, bed wetting, night terrors

Clinical Features

- Seizures (25-35%)
- Tic Disorders (9%)
- Mood abnormalities: depression, irritability, anxiety (25-40%)
- ADHD (30-75%)
- Self-injury

Clinical Features

- Sensory Integration Dysfunction
  - Visual
  - Auditory
  - Tactile
  - Gustatory
  - Olfactory

Genetics of Autism

- Familial cases are substantially more frequent. Sibling studies suggest 10-20% recurrence rate
  - Landau, Patterson, 2007
- Monozygotic twins (60-91%) Bailey et al, 1995
- Rett Syndrome MECP2 - X chromosome
  - Fragile X – synaptic gene regulation, 90% ASD
  - (Lord, 2006)
- Tuberous sclerosis -TSC1/TSC2
  - Neurofibromatosis—NF1
- 22q11.2 deletion- 20% with ASD features and 25% with schizophrenia

Genetics of Autism

- Neuroligins synaptic genes NLGN3 and NLGN4
  - cell adhesion molecules role of formation of functional synapses, X chromosome.
- SHANK 3, scaffolding protein of post synaptic density,chromosome 22
- Neurexins NRXN, presynaptic glutamatergic synapse, Chromosome 2p16, 11
- Single gene mutations, de novo Copy number variants, and common variant SNPS
- Cadherins, chromosome 5 Ubiquitin pathways

Synapse
Fragile X Syndrome: Inheritance

- X-linked disorder
- Both males and females can be affected or normal carriers
- Expansion of DNA insertion (CGG triplet repeat)
  - Normal carrier 25-200
  - Affected >200
- Amplification of triplet repeat in successive generations
- Reversible in mice 2008, MIT

Fragile X Syndrome: Dysmorphic Features

- Macrocephaly
- Prominent jaw (becomes evident in adolescence)
- Large, cupped, low set ears
- Long facies
- Increased joint flexibility
- Large testes (often not present until adolescence)

Tuberous Sclerosis

- Speech Language delays
- Behavioral problems
- PDD in 60% of affected children
- Epilepsy in all cases with dual diagnosis
Is there a neurobiological basis for disturbed sleep in children with ASD?

- **Serotonergic Abnormalities:**
  High levels of anxiety, tears and arousal levels (serotonin, 5HT2,3)

- **Dopaminergic pathways:**
  PSG- increased level of muscle twitching, muscle activity during REM, PLMS
  (Diomendi et al, 1999, Thirumalai, 2002)

- **Abnormal Melatonin Rhythm**
  There is emerging data involving the role melatonin plays in ASD and the efficacy of exogenous melatonin

Biology of Autism


- Specialized Face Region of the right hemisphere

- Neuro functional marker- hypoactivation of the FFA

- Function MRI- five studies -children and adults with ASD reduced activity to images of the human face.

What can nurses do? Screen

- **Early Warning Signs**
  - No Big Smiles or warm joyful expressions by 6 months
  - No back and forth sharing by 9
  - No babbling by 12 months

Screen!!

- No gestures by 18 months
  - pointing, waving, nodding, giving, showing

- No words by 16 months

- No two word phrases by 24 months, meaningful phrases

- Loss of skills at any age!!!!!!

Early Warning Signs: Behavior

- Severe prolonged tantrums
- Uncooperative or oppositional
- Doesn’t know how to play with toys
- Gets stuck on things over and over

- Persistent toe-walking
- Unusual attachments to parts of toys or objects
- Lines things up
- Odd movement patterns
- Extremely oversensitive to certain textures or sounds
Modified Checklist for Autism in Toddlers (MCHAT)

- Checklist for Autism in Toddlers/Modified CHAT
- Screen @ 18 months / 24 months in primary care setting
- CHAT: 9 questions/ 5 observations pointing, pretend play, joint attention
- MCHAT: 23 questions (parent report)
  - No observations (Robbins, Fine, Barton, 1999)
  - Free Google, forms available

Advantages of Early Diagnosis

- Earlier educational planning & treatment
- Family supports and training
- Reduce family stress and “shopping”
- Delivery of appropriate medical care - sleep
- Identify & treat target behaviors which interfere with progress
- Improved outcomes – function, behavior, language

Clinical Evaluation

- Hearing test
- Speech/language Evaluation
- Occupational/ Sensory Evaluation: gross and fine motor
- Psychological Evaluation
- Diagnostic Tools

Clinical Evaluation

- Autism Diagnostic Observation Schedule (ADOS)
  - Semi-structured observational assessment based on developmental language age
  - Investigator-directed activities to evaluate
    - Communication
    - Reciprocal social interaction
    - Play
    - Stereotypic behavior and unusual interests

What behaviors are we evaluating under each category of the DSM-IV?

- Social Interaction (ADOS)
  - Amount of eye contact
  - Facial expressions (multiple by 12 mo.)
  - Shared enjoyment in interactions (by 4 mo.)
  - Showing (by 12 mo.)
  - Spontaneous initiation of joint attention
  - Response to joint attention
  - Quality of social overtures

What behaviors are we evaluating under each category of the DSM-IV?

- Communication (ADOS)
  - Frequency of vocalizations directed to others
  - Stereotyped/diosyncratic use of words
  - Unusual vocal quality
  - Use of other’s body to communicate
  - Conversation
  - Pointing (by 12 months)
  - Gestures (by 12 months)
What behaviors are we evaluating under each category of the DSM-IV?

- Repetitive/Stereotypic Behavior
  - Unusual sensory interests in play material or person
  - Hand and finger and other complex mannerisms
  - Self-injurious behavior
  - Unusually repetitive interests or stereotyped behaviors

Treatments: “Standard”

- Educational - small class size –
- Individual Education Plan
- Behavioral
  - Applied Behavior Analysis/ Discrete Trial Instruction, Floor Time
- Speech/Language Therapy: Intensive PECS (Picture Exchange Communication System)
- Occupational Therapy - sensory integration-intensive

Educational Treatment

- Educating Children with Autism
  - www.nap.edu
- Early & intensive [>25 h/week]
- Objective assessment
- Curricula
- Skill generalization & maintenance

Behavioral Treatments

- APPLIED BEHAVIORAL ANALYSIS (ABA)
  - B.F. Skinner 1954
- DISCRETE TRIAL (DIR)
  - Ivar Lovaas
- GREENSPAN “FLOOR TIME”
  - Stanley Greenspan
- APPLIED VERBAL BEHAVIOR
  - Carbone, Partington, Sunberg
- SOCIAL STORIES
  - Carol Gray
- COGNITIVE BEHAVIORAL THERAPY

Token Economies

Speech/language Therapy

- Principles
  - increase eye contact; decrease non-communicative language; emphasis on pragmatics; use any effective modality
- PECS
  - Picture Exchange Communication System
- Sign Language
Sample Daily Schedule

Occupational Therapy
- Enhance upper extremity skills and visual motor
- Sensory Integration treatment controversial?
  - Addresses sensory abnormalities
  - Positive effects described as “systematic desensitization”

Sensory Integration Therapy

Medical Evaluation
- Dysmorphology exam: woods lamp
- Metabolic Studies: hypotonia, hypoglycemia
- Serum amino acid and/or urine organic acid [<5% with metabolic disorder]
- Thyroid function Tests, Lead level
- Electrophysiology: EEG, MEG
- Starring spells
- Neuroimaging: MRI, PET

Psychopharmacology
- Adjunct to educational, developmental & behavioral interventions
- Treat target symptoms
  - Sleep – insomnia, tantrums, irritability, hyperactivity, attention span, self-injurious behavior, aggression
- Enhance ability to benefit from behavioral interventions and optimize functioning

Psychopharmacology
- Stimulants
  - Inattention, hyperactivity
    - Adderall, Ritalin, Focalin Concerta
- Mood stabilizers
  - Agitation, aggression, acting out
    - Trileptal, Depakote, Topamax
- Blood pressure meds
  - Agitation, impulsivity, anxiety
    - Tenex, Clonidine, Intuniv
- Atypical Neuroleptics
  - Stereotypies, hyperactivity, aggression
    - Risperidol, Abilify, Seroquel
- SSRI (Selective Serotonin Re-uptake Inhibitors)
  - Obsessions, perseveration, anxiety
    - Prozac, Zoloft, Luvox
ADHD symptoms
- Inattention
- Impulsivity
- Hyperactivity
- Noncompliance
- Impulsive aggression
- Difficult Social interactions
- Deficits in Academic productivity and accuracy

Norepinephrine and Arousal
- Brennan and Arnsten describe the effects of catecholamines on the prefrontal cortex with the inverted U model. Too little or too much NE impairs prefrontal cortex (PFC) cognitive abilities.
- NE is also involved in the processing of sensory stimuli and can increase the "signal/noise" ratio of this stimuli (Brennan and Arnsten, 2008).
- This model provides a framework for deeper understanding the cognitive deficits and "hypo" and "hyper" arousal symptoms in children with ASD.

Locus Coerulus-Norepinephrine System
Dr. Rita Valentino

Arousal Dysregulation in ASD
- Arousal theories remain at the heart of clinician dialogue. Children with ASD have been described by clinicians and therapists as being either "hypo" or "hyper" aroused to internal and external stimuli.
- Hutt and colleagues in 1964 were the first to hypothesize that autism involved chronically high arousal levels.
- Dawson and Dewey (1989) described a general over-arousal and narrow range of optimal arousal in autism. These hypotheses have not been adequately investigated.
- Neurocognitive theories do not explain the third core set of symptoms:
  - Behavioral rigidity
  - Over or under responsiveness
  - Unusual reactions to sensory stimuli

Rogers & Ozonoff, 2005.

Norepinephrine and Arousal

Inverted-U Model

Cognitive function

AROUSAL

LOW

HIGH
Autism Spectrum Disorders

Behavioral Symptoms
- Withdrawn
- Unresponsive
- Sensory Seeking
- Depressed

LOW

AROUSAL

HIGH

Adequate Sleep

Insomnia

Alpha Agonists

- Tenex (Guanfacine) 0.25mg-1mg 2-3 x a day
- Clonidine 0.025mg ¼ Tablet 0.1mg every 4-5 hrs
- Intuniv 1mg -4mg XR guanfeciene

Advantages
- May be useful to treat very hyperactive or aggressive patient
- May improve ability to fall asleep
- May reduce tics

Disadvantages
- Less effective for inattentive symptoms
- Sedation
- Risk of adverse CV effects and depression

Baseline EKG

Stimulants

- Immediate release MPH (3-4 hr)
- Ritalin®, generic methylphenidate
- Dex-MPH (3-6 hr)
- Focalin®
- Intermediate-acting MPH (6-9 hr)
- Metadate CD (30/70)
- Ritalin® LA (50/50)
- Long-acting MPH (up to 12 hr)
- Concerta
- Focalin XR
- Daytrana

Amphetamines

- Short-acting AMP - 4-6 hour
  - Dexamphetamine®, DextroStat®, generic dextro-amphetamine
- Intermediate-acting AMP - 6-8 hour
  - Adderall®, Dextroamphetamine® spansules, generic mixed salts of amphetamine, Vyvanse
- Long-acting AMP - 10-12 hour
  - Adderall XR®
  - Vyvanse

American Heart Association Report
Stimulants and Cardiac Risk:

- Careful history emphasizing personal and family history of heart disease
- Careful physical examination
- Baseline EKG (current EKG for those already on stimulants)
- Importance of sudden cardiac death registry

Anxiety/OCD

- Repetitive behaviors or thoughts
- OCD behaviors
- Difficulty with transitions
- Extreme need for routine
- Anxiety / Hyper arousal
Selective Serotonin Reuptake Inhibitors

- Prozac 1mg- 40mg
- Zoloft 5mg- 200mg
- Luvox 12.5mg- 250mg

Risperidone

FDA approved

Receptor sites
- 5HT 2 A and T7
- Alpha agonists 1 and 2
- Dopamine 2
- Histamine
- 0.1 mg up to 4.6 mg

Anti-Convulsants /Mood stabilizers

- Moody, fast mood swings
- Crying, laughing (no reason)
- Easily frustrated without antecedent
- Abrupt violent aggression

Anti-Convulsants /Mood stabilizers

- Depakote (valproic acid)
- Tegretol- 2nd generation Trileptal
- Topamax
- Lamictal
- Benzodiazapene - ativan

Predominant Sleep Disorders in ASD

Behavioral Insomnia- Sleep- Onset type
- Limit setting
- Sleep association

Insomnia due to Pervasive Developmental Disorder
- Abnormal Melatonin
- High Arousal?
- Anxiety ?

Hyper-Arousal in Insomnia

- Current thinking on insomnia in Sleep Medicine regards the disorder as one of hyper-arousal.
- Early work: Internalization of emotional arousal (Monroe, 1967)
- Cognitive arousal theory hypothesis:
  - increased cognitive activity: thinking and worrying while trying to fall asleep prevents the initiation of the sleep process (Borkovec, 1982 Harvey, 2002)
- Cognitive Behavioral therapy-Insomnia

Melatonin

- A powerful antioxidant molecule, involved in the regulation of circadian and seasonal rhythms
- Modulates neuronal plasticity, regulates circadian gene expression and immune function
  - El Sherif, et al 2003
- Key role in communication behavior, song learning in birds
  - Janzen et al 2005

Daytime Sleepiness

- Increased seizures? Wasdell, 2008
- Effect on the CNS and direct Hypothalmus and pituitary gland action
  - Pang et al 1998
- Nature’s contraceptive, photo periodic control in animal reproduction, survival of the species
  - Pang, et al 1998
- Alterations in LH and FSH with melatonin level in the rat and ewe
- Gonads: target site of melatonin action in ducks and chickens
  - Ayre & Pang, 1994

Recommendations

- No practice guidelines at the Regional Autism Center
- Benefit/risk ratio on a case by case basis
- Sleep hygiene and behavioral interventions should be tried first
- Melatonin start slow, increase dose by 0.3mg?
- UMMC web site recommends starting at 0.3mg, liquid preparation and increasing slowly
- Synthetic melatonin, pharmaceutical grade
- Avoid possible animal contamination
- Reputable company, with quality control systems
Complementary and Alternative Treatments

- Vitamin A, C
- B6 and Magnesium
- DMG [Dimethylglycine]
- Diet: Casein/ gluten free; other elimination
- Immunotherapy
- Yeast/ Antifungal therapy
- Secretin
- Antibiotics/ Antivirals
- Hyper baric therapy

Family Support

- Early Years
  - Seeking a “Diagnosis”
  - Finding therapists
  - Family balance
  - Financial Cost
  - Bonding

- School Age Years
  - Physical demands/time demands
  - Employment
  - Social isolation
  - Role restrictions
  - Strain on marriage
  - Respite care

- Teen/Adult Transition
  - Sexuality
  - Safety
  - Services “What do I do when the school bus doesn’t come anymore?”
  - Respite Care
  - Residential placement
  - Job training/ Life skills coaching

Thank you