Atypical Behaviors in Autism – Diagnostic Implications

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Pervasive Developmental Disorders - DSM IV (1994)

- Autism
- Asperger’s Syndrome
- Rett Syndrome
- Childhood Disintegrative Disorder
- Pervasive Developmental Disorder - not otherwise specified.
DSM-V (2013)

• Asperger’s syndrome removed as separate
• Asperger’s syndrome now subsumed under the Autism Spectrum Disorders (ASDs)
• ASD categorized as mild, moderate, severe.
• New category of Social Pragmatic Disorder.
• How might this change impact service provision and clinical research going forward?
Core features of Autism

• Impaired social interaction
• Delayed and disordered language
• Isolated areas of interest
Inconsistent Clinical Features

- Atypical prosody, intonation
- Echolalia, scripting, pronoun reversals
- Repetitive and stereotypic behavior
- Need for routine; difficulty with novelty
- Hypotonia, poor motor coordination
- Atypical information processing
- Sensory dysfunction
Infant Toddler Data-Baby Sibs Studies

- The socially serious baby
- Decreased social reciprocity
- Limited babbling/vocalization.
- No pointing for communication at 12 months
- Absent joint attention at 12 months
- Limited or absent imaginary play
- Visual gaze
- The presence of head lag at 6 months
Baby Autism Sibs data - cont.

• Atypical motor patterns
• Abnormal response to maternal “still face”.
• “Is this baby like the last one?”
• Earliest diagnosis now at 12-14 mos. Can we do better without a biomarker?
• Diagnostic “stability” said to be 30-34 mos. The time when a diagnosis can be certain.
Possible Etiologies

- Genetics/epigenetics
- Infection - bacterial/viral
- Environmental factors - vaccines, mercury, MMR, dietary factors, toxins, endocrine disruptors, paternal age, prematurity, other.
- Immune/autoimmune factors.
- Current consensus - ASD is heterogeneous clinically, biologically and etiologically.
Neurological Assessments of the Child with Autism

1. Obtain a medical and developmental history

2. Neurological examination and behavioral observation

3. Consider need for additional studies:
   a. Chromosomal/DNA analysis
   b. Electroencephalogram (EEG)
   c. Imaging studies (MRI, CT)
   d. Metabolic (blood/urine) studies
What have we been missing?

• ASD classically defined on the basis of cognitive, behavioral, language and processing modalities.

• But ASD may be more than a disorder of information processing, language and behavior.

• ASD children, adolescents and adults can and often do have medical issues that have largely gone unrecognized and unaddressed.
Disruptive Behaviors

• Atypical and/or disruptive behaviors of varying descriptions and severity have often been seen as just “part of the Autism”.

• But are they???
What is the definition of “behavior”?

• The manner in which an organism behaves in reaction to social stimuli or inner need.

• Observable activity in response to an external or internal stimulus.

• Anything that the organism does that involves action or response to stimulation.
What do we know?

- Research indicates that typically developing children often show elevated rates of problem behavior in association with physical illness.

- Physical illness is common in persons with developmental disabilities (DD).

- Studies have documented significantly higher rates of acute and chronic medical conditions in DD persons as compared to the general population.
What medical conditions have been documented?

• Problem behaviors have been linked to conditions such as constipation, allergies, premenstrual syndrome, ear infections and urinary tract infections.

• Plausible explanation relates to degree of pain or discomfort experienced by the individual at the time rather than to the physical illness per se.
Monitoring pain & discomfort is a complex process

- DD persons often lack the communicative and cognitive skills that would allow for the direct assessment of pain and discomfort using a patient scale, checklist and/or interview strategies.

- Recent data suggests that those with the most severe cognitive impairment and fewest communication skills are likely to experience the most pain over time (Breau et al., 2003)
Why have these been overlooked?

1) Longstanding assumptions about what autism is and who ASD persons are. Abnormal behaviors often interpreted as part of the clinical profile of the disorder.

2) ASD individuals may not present with the same symptoms or “red flags” as their “neurotypical” peers. Medical history may not help us.

3) Many ASD persons cannot tell us if they hurt/are uncomfortable nor accurately localize discomfort.
Weak Insights into Overall Health Issues

- Difficult to see beyond cognitive or behavioral features of the disorder
- Limited research into physiology of other organ systems outside of the brain in ASD
- Limited vehicles for collaboration on health issues
- No uniform set of clinical measures or data base.
Associated Medical Concerns?

Seizures
Sleep disturbances -
Headaches
Gastrointestinal disorders
Genitourinary
Hormonal imbalance/endocrine dysfunction
Metabolic Disorders
Seizures - are they real?

- Often hard to tell - presentation may be atypical
- Routine EEG may not be helpful
- More prolonged EEG by high quality lab may help - the study is only as good as the person who interprets it.
- Use of video monitoring, MEG, other.
- Use of video taping
Sleep Disorders

- Problems with sleep onset or staying asleep
- Is this coming from the brain (centers of arousal)?
- Is this due to GI disorder? Acid reflux?
- Is this a respiratory problem? Does the child mouth breath suggesting big tonsils/adenoids?
- Sensory integration issues - needs deep pressure?
- Allergies, eczema?
Gastrointestinal Disorders

- Chronic diarrhea or constipation
- Feeding/eating disorder
- Change in sleep patterns
- Parents concerned about food allergies, need for special diet, yeast
- Possible abdominal pain/discomfort
- Behavioral changes or increased severity.
Neurotransmitters

• Every known neurotransmitter present in the brain is present in the gut
• Acetylcholine, GABA, dopamine and serotonin have been connected with ASD
• All affect GI motility and sensitivity in a variety of ways.
Clinical Signs of GI Disorders

- Gulping and facial grimacing
- Tapping on the chest or stomach
- Putting pressure on the abdomen
- Constant chewing on non-edible items - shirt sleeves, shirt neck lines, etc
- Frequent eating/drinking
- Any unexplained negative behavioral change, including aggression, self-injurious behavior, with or without GI symptoms.
Take Home Message

• ASD children, adolescents and adults, even if they have some language/words, should be evaluated for possible GI disorders - IF they present largely or exclusively with behavioral symptoms, including sleep disorders.
• ASD patients may not present with the usual GI symptoms.
• Do NOT assume that all behaviors are “behavioral” or psychiatric in origin.
• Prevalence rates of GI disorders in ASD said to be 20-80% depending on study. We really don’t know.
the MET Gene

- Campbell et al., March 2009, Pediatrics
- MET gene associated with ASD
- MET gene expression decreased in temporal lobe of brain in ASD
- MET is a pleotropic receptor that functions in brain development, in the immune system and in GI repair.
MET Gene

- Study of 214 families within the AGRE registry with Essential ASD and complete GI histories.
- 992 subjects from the 214 families were studied.
- ASD with GI symptoms - 41%
- Parents - 24%
- Unaffected siblings - 9%
MET Gene

• Of the 214 families, 118 had at least one child with co-occurring ASD and GI symptoms. MET allele c was associated with co-occurrence in the entire sample.

• 96 families did not have co-occurrence. No association with MET gene in this group.

• Thus, MET signaling may define a subset of ASD and co-occurring GI disorders.
MET Gene

• Data is consistent with the hypothesis that genetic risk that underlies disruption of a single cell signaling system, can lead to independently generated brain-based and systemic dysfunctions that ultimately interact to influence long-term pathological processes.
Endocrine/Hormonal Disorders

• ASD girls whose behavior worsens with onset or during adolescence.
• Many found to have imbalance between
  progesterone and estrogen. Can be treated.
• Small subset with Congenital Adrenal Hyperplasia
• Should we also be looking at teenage ASD boys?
Reason for GU referral

• Previously continent child becomes incontinent
• Usually a preteen
• May be a “spastic bladder”
• Treatment with Ditropan may be helpful
"Red Flags" for Metabolic Work-up

- Poor physical endurance
- Late walking (i.e. 24 months)
- Repeated regressions after age 2 1/2 years
- Dysmorphic features
- Making poor progress despite excellent services
- Qualitatively “different”
- Involvement of multiple organ systems
Mitochondrial Disorders

- Weissman, et al., December 2008
- 25 patients with ASD
- All later determined to have enzyme or mutation-defined mitochondrial dysfuntion.
- 21 subjects had non-neurological medical problems
- 19 subjects had constitutional symptoms, primarily excessive fatigue
Mitochondrial Disorders

- 32% - delayed motor milestones
- 40% - unusual patterns of regression
- 76% - abnormal levels of blood lactate
- 36% - abnormal levels of blood alanine
- 52% - abnormal levels liver function studies
- Most common electron transport chain disorders were Complex I (64%) and Complex III (20%)
Mitochondrial Disorders

• Although initially all subjects were identified as having Essential (Idiopathic) Autism, careful clinical and biochemical assessment identified features that differentiated them from children with Idiopathic Autism.

• This preliminary data suggests that a disturbance in mitochondrial energy production may underlie pathophysiologic mechanisms in a subset of ASD persons.
Psychopharmacology

• Approach to medication management
  – Rule out potential medical disorders first
  – Should never be first line of defense - should be used as an adjunct to other interventions.
  – Consider specific symptoms - depression, anxiety, OCD, impulsivity, ADHD, etc
  – Consider the risks and benefits of choosing and using any medication.
Psychopharmacology

- Family should find a psychopharmacologist with whom they are comfortable.
- Choice of medications may be influenced by training of provider.
- Health care insurance may influence choice of medication.
- Consider medical risks, cost to the patient, potential invasive procedures (blood draws), tolerance of side effects, possible drug interactions and methods of administration.
Other medical conditions

• Obesity
• Osteoporosis
• Otitis media
• PANDAS
• LYME Disease
• Dental
• Injuries/fractures
Controversial Therapeutic Approaches

- Allergies and yeast
- Gluten/casein free diet
- Applied Behavior Analysis
- Sensory motor Integration
- Auditory training
- Immune Therapy/IVIG
- Chelation
- Secretin
- Facilitated communication
- Vitamin/dietary supplements
- Fast ForWord
- Hyperbaric oxygen
- Floor Time (Greenspan)
Gluten and Casein Free Diet

- Preliminary study from University of Rochester
- Presented at IMFAR in May 2010
- Small number of subjects (18 families)
- Investigators supplied food to all families
- Study was double blinded
- No differences in development, behavior, cognition, language.
ASD individuals need/deserve appropriate medical care.
May not present with typical symptoms.
Changes in behavior or prolonged episodes of behavioral abnormalities merit a medical look.
Many of these disorders are treatable.
We need to learn the language and signs of pain/discomfort in non-verbal and sensory impaired ASD individuals.
The Autism Treatment Network (ATN)

Began in fall 2003. Modeled after LADDERS multidisciplinary/interdisciplinary program

Originally consisted of five academic sites
– U. Wash (Seattle), Baylor, Columbia, OHSU, MGH

Involves multidisciplinary medical teams
Involves use of common protocols
Commitment to data sharing across/between sites
Why a consortium?

• Evaluate potential “red flags” - are they valid?
• Are there other “red flags” as yet to be identified?
• What proportion of ASD population affected?
• Accurate identification of medical disorders
• What interventions are most effective?
• Establish scientifically sound and meaningful standards of care
Where are we now?

• In January 2007 and again in 2013, Autism Speaks initiated a Request for Proposals - to expand the ATN initiative
  – As a result, there are now a total of 14 multidisciplinary medical sites associated with academic centers.
  – Sites are providing standard medical assessments and care for ASD persons, sharing protocols and submitting data into a common database. Medical studies can be funded by ATN and AIR-P.
ATN Sites -2014

- Alberta, CA  U. Missouri, Columbia, MO
- Arkansas      U. Pennsylvania, Philadelphia
- Cincinnati    U. Rochester, NY
- Denver        UC Irvine, California
- LADDERS.LFAC  USC
- Nationwide Childs  Vanderbilt
- Pittsburgh
- Toronto, CA
ATN Projects – past and present

- GI studies - constipation
- Sleep studies
- Nutrition studies - GFCF diets
- Bone density studies
- Creatine deficiency disorders
- Quality of life
- EEG analysis in ASD baby sibs - ?biomarkers
Goals of the ATN

• To establish evidence based data with regard to medically related conditions in ASD.

• To establish standards of health care for children, adolescents and adults on the spectrum.
Summary
Medical Co-morbidities are important

• Improve quality of life.
• Better health leads to better outcomes.
• Subsets of ASD persons may be more specifically identified - genetically and/or metabolically.
• Understanding associated medical conditions could enhance our understanding of the neurobiology of ASD.
• THERE IS HOPE

• Early diagnosis and intervention result in improved outcomes.
• Some ASD children lose their diagnosis
• Rx for medical disorders results in better outcomes
• Identification of ASD subsets
• Better availability of services
• Some symptoms improve with age (adults)
Future Directions

• Efforts to identify diagnostic biomarkers
• Identification of ASD subsets
• Expansion of use of assisted technology
• Explicit correlation between imaging and postmortem brain studies and clinical phenotypes
• Longitudinal studies in same population

What is the natural life history of the disorder?
Future Directions – cont.

• Correlations between genetics and clinical phenotypes. Differences in males vs females.
• Studies of the gastrointestinal and brain connections. Studies of the microbiome.
• Meaningful employment for ASD adults
• Studies of aging – where are the ASD seniors? Is ASD “progressive”?