Defining and Treating Autism: Considerations for Biomarkers in Research and Clinic

Martha Herbert, MD, PhD
Pediatric Neurology/Center for Morphometric Analysis
Center for Child and Adolescent Development
TRANSCEND Research Program
Massachusetts General Hospital and Cambridge Health Alliance
Harvard Medical School
Why biomarkers in autism?

• Diagnosis
• Identification of pathophysiological mechanisms
• Subgroup
• Identification of treatable features
• Predict/track treatment response

Overall NEEDS:
• Focus on BIOLOGY, PATHOPHYSIOLOGY
• Coordinate measures across levels
Pathophysiological MECHANISMS: The “Middle-Out” Approach

**Strongly Genetic, Modular Brain-Based Model**

From

Gene → Brain → Behavior

To

Pathogenesis

Gene/Environment; Epigenetics

Altered Molecular and Cellular Mechanisms → Altered Tissue, Metabolism → Altered Connectivity and Processing

MECHANISMS

Genetically Influenced, Systems/Systemic Model

Observables phenotype

Behavior, Cognition, Sensorimotor, Somatic symptoms

Herbert, 2005
Multi-system from the start? Kanner 1943 on somatic symptoms

Case 1: “Eating has always been a problem …..” for him. He has never shown a normal appetite.”

Case 2: “…large and ragged tonsils.”

Case 3: diarrhea and fever following smallpox vaccination …. healthy except for large tonsils and adenoids.

Case 4: vomited a great deal during his first year… feeding formulas were changed frequently … tonsils were removed…

Case 5: nursed very poorly … quit taking any kind of nourishment at three months… tube-fed five times daily up to one year of age…At camp she slid into avitaminosis and malnutrition but offered almost no verbal complaints.”

Case 7: vomited all food from birth through the third month….

Case 8: feeding formula caused …concern. … colds, bronchitis, streptococcus infection, impetigo…

Case 9: none of the usual children’s diseases.” [? Overactive immune system?]

Case 10: frequent hospitalizations because the feeding problem … repeated colds and otitis media

Case 11: was given anterior pituitary and thyroid preparations for 18 months

Kanner, discussed in Jepson 2007
Pathophysiology requires understanding the brain as an organ in the body that can get sick.

**Pathogenesis-Brain:**
Targeting based on physical properties (receptors, growth factors, etc.)

**Brain-Behavior:**
Behavior modulated by regional and neural systems alterations

**Pathophysiology**
(including metabolism, immunology, metabolic imaging, neurology, systems neuroscience)

**Cognitive Neuroscience**
(including psychology, linguistics, functional neuroimaging, systems neuroscience)

**NEED:**
Programmatic Brain-Body Biomarker Linkage

Herbert & Ziegler, Neurotoxicology, 2005

In 36 years:
78 articles out of 2004
(average ~2/year)
45 substances studied

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<th>Biomarkers Tested</th>
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**Legend**

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New Frontiers: THE METABOLOMOME CONCEPT
Biomarker challenges in autism: Critical issues

• Variable severity
  – Striking “good hair day, bad hair day” changes

• Chronic features
  – Oxidative stress, inflammation, metabolic perturbations are ongoing

• Treatment-responsiveness
  – Stable improvement can follow treatment

• Multi-system—gut, immune, sleep, metabolism, more
  – Is impact on brain primary, parallel or downstream?

• Heterogeneity
  – Where are commonalities & final common pathways?

• Chronic pathophysiological features appear non-specific
  – Some important potentially treatment-responsive features are non-specific to autism
Biomarker challenges in autism: 

**NOT a “static encephalopathy”**

- **Variable severity**
  - *Transient improvement w fever* (Zimmerman A Pediatrics in press)
  - *Spikes in function in stress or emotional situations*
  - *Transient improvement on antibiotics* (Sandler, Finegold, Bolte, JCN 2000)
  - *Improvement on allergy medications*
  - *Variability in function related to food, allergen and toxic exposures*

- **Treatment-responsiveness**
  - *Stable improvement can follow treatment*
  - *Published reports of loss of diagnosis* (Fein D –Sutera, Kelley in JADD ’06 & ’07)
  - *Recovery documentation studies in process*

**Neurobiological Implications:**

**NEUROMODULATORS, not just wiring**
Not just human metabolism: Abnormal Clostridial bacteria species in autistic children’s stool.

What we NEED: **Extended Metabolome** for subtyping

Finegold S, 2002

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9 Clostridial species in stool from autistic children not in controls

3 clostridial species in controls not in autistic children

Abnormal gut flora metabolism can

- deplete vital nutrients
- alter metabolism of xenobiotics

This can cause or worsen metabolic stress.

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See also: **Host and gut-microbial co-metabolome interaction**

J Nicholson, Nature Reviews Microbiology, 2005
The Every Day of Some Autisms

What we need:
Clinical labs that will detect and report pertinent gut pathogens
Two reasons measurements need to be coordinated across levels

1. Heterogeneity at multiple levels: Where is the commonality?

Pathogenesis
Gene/Environment; Epigenetics

MECHANISMS
Altered Molecular and Cellular Mechanisms
Altered Tissue, Metabolism
Altered Connectivity and Processing

Observable phenotype
Behavior, Cognition, Sensorimotor, Somatic symptoms

2. Clinical vicious circles with amplifying feedback loops across levels

Toxics
Infection/Immune
Genes
Conclusion I: METABOLISM AS CORE FOCUS

**What we know**

- Environmental factors perturb metabolism even at low levels of exposure
  
- Some of the same mechanisms/pathways get hit, but spectrum and intensity of effects differs
  - Multi-system and multi-level impacts

- Metabolism is target for biomedical treatments

**What we need:**

- Study how “Environmental perturbation of metabolism” has different patterns and thresholds than “inborn errors of metabolism”
Conclusion II:
What we know:
Metabolism is complex and variable
What we NEED:
Strong Infrastructural Support to *meet the challenge*

- **Biomarker/metabolite consensus meetings**
  - Identify a core of measures less sensitive to state and handling
  - Consider “Omics” and other profiles
    - Metabolomics; Extended Metabolomics (gut metabolites)
    - Other –Omics—nutrigenomics, toxicogenomics
    - Organic and amino acid profiling
    - Cytokines, chemokines
  - **SOPs**—Standard Operating Procedures
  - Special focus on environmentally responsive metabolism
- **Repository** with multi-center participation
  - Encourage contributions from research projects with well-phenotyped subjects
What we know: Brain and metabolism are abnormal
What we need: Learn how metabolism modulates brain (and vice versa)
This requires integration.
Integration requires infrastructure.

- Brain tissue characterization
- High temporal resolution brain function measures (MEG, EEG)
  - closer to metabolically vulnerable synaptic (dys)function
- Systemic metabolic characterization
- Extended metabolome (gut microecology)
Conclusion III:

*What we know:* Change and Treatment are possible

*What we need:* Better tools to track treatment and change biologically

Repeated measures in same individuals to see what can change

- Individuals to study
  - Individuals over time
  - Children at risk for autism
  - Children undergoing treatment
  - Good-hair vs. bad-hair days

Subgrouping

- Identify mechanisms
- Predict treatment response

Matson
Conclusion IV:

**What we know:**
One biomarker for autism is unlikely.

**What we need:**

*Profiles of Vulnerability and Treatability*

- Environmental perturbation of metabolism is widespread and can be missed by existing reference ranges

- Autism’s *sensitive physiology* may mean trouble for the individual even when labs are within the population “normal” range
Beyond characterizing autism, the point is to treat it!