The Epidemiology of Autism: Investigating Perinatal Risk Factors

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Overview of Presentation

- What is epidemiology
- Epidemiology of autism
- Immune function and autism
- Future directions
What IS an Epidemiologist Anyway?

We don’t study bugs!
Epidemiology is...

- The study of patterns of health and illness at the population level
- The identification of risk factors for disease
- It informs public health prevention strategies
- Ultimately leads to optimal treatment approaches at the individual level
How to Be an Epidemiologist in Three Easy Steps

Step 1: Define
- What is it?

Step 2: Describe
- How many people are affected?
- Who is affected?
- Where does it occur?
- When does it occur?

Step 3: Analyze
- Why does it happen?
- What are the risk factors? causes?
Step 1: Define
What is autism?

- Persistent deficits in social communication and social interaction across multiple contexts
- Restricted, repetitive patterns of behavior, interests, or activities
- Symptoms must be present in the early developmental period
- Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
- These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.
Step 2: Describe
Autism Spectrum Disorders (ASDs)

1 in 59 children living in ADDM sites are identified with ASD

Year

Kanner
Rutter
DSM-III
DSM-III-R
ICD-10
DSM-IV

1990 2000 2010 2020
Step 3: Analyze
Investigating relationship between Exposure and Outcome
Refrigerator Mothers
Prenatal Origins of Autism

Brain Structures and Function as They May Relate to Autism

- **Basal Ganglia**
  - Motor planning and execution

- **Frontal Lobe**
  - Representation of action plans
  - Motor planning and execution

- **Amygdala**
  - Recollection of affective significance of smell or taste
  - Perception of body movements
  - Sensitivity to social stimuli
  - Production of goal-directed behavior

- **Cerebellum**
  - Hypotonia in infancy

- **Hippocampus**
  - Learning and memory

Adapted from: Zimmerman and Gordon, 2000

Rubella & Pregnancy

Kaiser Permanente
Autism Etiology: Genes And Environment

- Combination of genetic and environmental factors
- Critical exposure window is very early in development
- Different clinical subgroups likely have different risk factor profiles
Conceptual Model of Autism Etiology

- Environmental Factors
- Genetic Factors
- Immune
  - Endocrine
  - Metabolic
  - Epigenetic
- Behavioral
- ASD
- Developmental
- Medical
The Immune and Nervous Systems

Immune System
• Body’s natural defense mechanism
• Detection of wide variety of foreign agents

Nervous System
• Transmit signals between different regions of the body
• Interactions between complex neural pathways
• CNS: brain and spinal cord
• PNS: sensory neurons

Neuroimmunology
• Complex interactions between the two systems:
  • during homeostasis
  • response to injury
  • development

Key factors
• Cytokines/chemokines
• Immune signaling pathways
• Antibodies
Immune Function in Autism

- Genes that regulate immune response
- Abnormal immune markers in peripheral blood of children with ASD
- Neuroglial activation and neuroinflammation in brain and CSF
- Infection, asthma, allergies in children with autism
Are immune changes...
Maternal Immune Function

Postnatal Period

- Maternal history of autoimmune disease
  (Comi 1999, Sweeten 2003)
- Autoantibodies in serum/plasma to fetal brain proteins
  (Braunschweig 2007; Zimmerman 2007)
Maternal Autoantibodies to Fetal Brain Postnatal Serum

Postnatal serum from mothers of children with autism (AU), developmental delay (DD) and typical development (TD).

Reactivity of maternal IgG against human fetal brain proteins by western blot.

Braunschweig et al, 2007
Maternal Immune Function

Prenatal Period

• Infection, asthma, allergy, autoimmune disease during pregnancy

• Altered patterns of inflammatory markers in prenatal serum and amniotic fluid (e.g., cytokines)

• Autoantibodies in prenatal serum to fetal brain antigens
Prenatal Infection and Autism Spectrum Disorders in Childhood: A Population-Based Case–Control Study in Taiwan

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Abstract

Background: Infection in pregnancy has long been linked with negative postnatal development and health. This study aims to assess the association between prenatal infections and autism spectrum disorders (ASDs) across three trimesters and to probe possible sex heterogeneity in such link.

Method: A total of 4184 children with incident ASDs and 16734 matched children were identified from the 2006–2007 National Health Insurance Research Database. For each child, information pertaining to the mother’s infection during pregnancy, sociodemographics, and medical history was retrieved from healthcare records. Conditional logistic analyses were carried out to estimate the strength of associations with adjustment for multiple comparisons.

Result: Pooled analyses demonstrated that having two or more outpatient visits for genital infection [adjusted odds ratio (aOR): 1.34; 95% confidence interval (95% CI) 1.12, 1.60; false discovery rate (FDR) < 0.01] and bacterial infection (aOR: 1.24; 95% CI 1.06, 1.43; FDR < 0.05) in the third trimester were slightly associated with increased risk of ASDs. No statistically significant sex differences were found.

Conclusion: The present study contributes updated population-based evidence about the connection between prenatal infection and ASDs. Potential effect of bacterial and genital tract infections during the third trimester on risk of ASDs warrants further exploration.

Keywords: autism, children, prenatal infection, sex differences.
Maternal Infection and ASD

- Several unanswered questions:
  - Which infectious agent? Viral? Bacterial? Parasitic?
  - Timing? 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} trimester?
  - Infectious agent vs immune response?
    - Fever?
      - increased production of cytokines directly or indirectly impacting the developing fetal brain?
  - Common underlying genetic susceptibility?
Maternal Autoimmune Diseases and ASD

- Similar story:
  - Most studies show an association
  - Specific autoimmune diseases vary
  - Timing during pregnancy varies
  - Autoimmune disease vs immune response?
    - increased production of cytokines directly or indirectly impacting the developing fetal brain?
    - Autoantibodies?
  - Common underlying genetic susceptibility?
Early Markers for Autism Study (EMA)

Investigating early biologic markers of susceptibility and exposure from critical periods of fetal brain development.

Determining etiologic contribution from immunologic and genetic susceptibility factors, environmental exposures, and the interplay of genes with environment.
Early Markers for Autism Study (EMA)

- Population-based case-control study of mother-baby pairs
  - Phase 1: ~80 ASD, 50 DD, 160 Controls
  - Phase 2: ~ 400 ASD, 400 DD, 400 Controls
- Prospective collection of
  - Maternal second trimester blood
  - Newborn peripheral blood
EMA Study

- Prenatal Organochlorines
  - Hazardous air pollutants
  - PBDEs
  - PFCs

- Genome-wide SNPs, CNVs
  - Mom and Child

- Cytokines, chemokines, CRP, Immunoglobulins, Autoantibodies

- Developmental
- Medical
- Behavioral ASD

Kaisers Permanente
Early Markers of Autism Study (EMA) – Phase 1

*Immune system factors associated with ASD risk*

**Maternal autoantibodies**  
(Croen et al, 2008)

**Maternal cytokines**  
(Goines et al, 2011)
Maternal Autoantibodies to Fetal Brain Prenatal Serum

Lane A: Autism with early onset phenotype with 39kDa: 73 kDa band pattern.

Lane B: Autism with regressive phenotype with 37 kDa: 73 kDa band pattern.

Lane C: Typically developing control child with no reactivity to fetal brain.
Maternal Prenatal Cytokine Profiles - Phase 1

- IFN-γ, IL-4, and IL-5 elevated in mothers of children with ASD (M-ASD) compared to mothers of control children (M-GP)
- IFN-γ, IL-4, and IL-5 levels were highly correlated
IL-6 elevated in mothers of children with DD compared to mothers of children with ASD and GP.
Maternal Mid-Gestation Cytokine Elevation: What Does This Mean?

- Increased IFN-γ, IL-4, and IL-5 is consistent with an allergy/asthma phenotype.

- Placenta forms a barrier between maternal and fetal circulation, though maternal immune factors including IgG and IL-6 are permitted to cross.

- Even if direct passage is blocked, maternal immune components may react with placental cells that may then alter the fetal compartment.

- This may be the case for IFN-γ, IL-4, and IL-5, which are not known to cross the placenta.
Mothers of children with ASD+ID had elevated inflammatory T cell and innate immune cell cytokines and chemokines.

These are normally downregulated during midgestation.

Suggests a lack of typical immune regulation during pregnancy.

Red = increased risk
Blue = reduced risk
EMI Phase 2 - Ongoing Analyses

- Other immune markers – autoantibodies, C-reactive protein
- Environmental exposures – PBDE, PCB, Pesticides, Air pollution
- Maternal and child genetic factors – GWAS, MET

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Graph showing relationships between various factors:
- Prenatal
  - Organochlorines
  - Hazardous air pollutants
  - PBDEs
  - PFCs
- Genes
  - Genome-wide SNPs, CNVs
    - Mom and Child
- Behaviors
  - ASD
- Developmental
- Medical

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Note: The diagram includes multiple interconnected nodes and arrows indicating relationships between different factors.
what's next
Unique Autism Research Opportunity at KP

- Diverse Membership
- Clinical Providers (clinicians, hospitals, clinics, laboratories, pharmacies)
- Longitudinal Medical Records
- Insurance System
- Biospecimen Repository

Research
Kaiser Permanente Northern California (KPNC)

- Group practice prepaid integrated health program
- 4.3 million patients
- 9,000 physicians
- 21 hospitals
- Fully electronic health record
- Serves ~30% of population in geographic region
### KPNC ASD Prevalence in June 2018

<table>
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<tr>
<th>Age Group</th>
<th>Number of ASD Patients</th>
<th>Prevalence per 1,000</th>
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<tbody>
<tr>
<td>0-4 years</td>
<td>2,827</td>
<td>13.4</td>
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<tr>
<td>5-9 years</td>
<td>5,984</td>
<td>26.2</td>
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<tr>
<td>10-14 years</td>
<td>5,439</td>
<td>22.3</td>
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<tr>
<td>15-17 years</td>
<td>3,046</td>
<td>20.7</td>
</tr>
<tr>
<td>18-24 years</td>
<td>5,007</td>
<td>13.9</td>
</tr>
</tbody>
</table>
KPNC Pregnancy Cohort
KPNC Pregnancy Cohort

- ~25,000 enrolled pregnancies
- ~21% overall response rate
- ~78% of participants provided 2 samples
  - 1st trimester samples received at 10 weeks
  - 2nd trimester samples received at 18 weeks
- ~25% completed the survey
- Participants are representative of KPNC prenatal population
IMPaCT - Immune and Metabolic Markers during Pregnancy and Child Development

Central hypothesis: Maternal inflammation during pregnancy stemming from immune or metabolic dysregulation will adversely impact child neurodevelopment. Further, the timing during pregnancy is important with respect to the specific neurodevelopmental outcome.

Objective: Conduct a longitudinal prospective analysis of maternal gestational inflammatory conditions and their genetic underpinnings in the context of neurodevelopmental outcomes in the child.
IMPaCT Study

Maternal characteristics

Immune profile
Metabolic profile

Neuro-developmental Disorders

Maternal genetic profile
Why is this important?

- We hope to identify patterns of maternal health conditions and biomarkers that indicate risk for specific child neurodevelopmental outcomes.
- Early identification could lead to earlier intervention and the possibility of preventing future morbidity as well as improving quality of life.
- The identification of biomarkers for prenatal risk will shed light on the biologic mechanisms underlying aberrant neurodevelopment, providing an opportunity for developing preventive strategies.
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