The Problem

- Every 5 minutes, someone is being diagnosed with debilitating deficits in:
  - communication & language use
  - social interaction and behavior
  - stereotypic or repetitive movements
- No established biological markers – behaviorally diagnosed
- Acquired while in-utero or up to 18 months old.
- A common disease of unknown cause, few treatment options, and too few community/educational/medical resources

A great social cost

- Lifetime cost of caring for a child with autism ranges from $3.5 to $5 million.
- United States is facing approximately $137 billion annually in costs for autism.
- $200-300 billion dollars in 10 years

Autism more prevalent than other top childhood diseases

- Estimates are derived from NIH and CDC sources

A common disease of unknown cause and steadily increasing rates

- Autism can’t be ignored
  -Lifetime cost: approximately $137 billion annually in costs for autism.
Synthetic organic chemical production, United States, 1945 - 1985

Source: U.S. Intern. Trade Commission

Chemical Intolerance

- About 5-15% of people report multiple chemical intolerances
- “Do you consider yourself sensitive to everyday chemicals like those in household cleaning supplies, paints, perfumes, soaps, garden sprays, or things like that?” (15%)
- Frequently, intolerances also include foods, medications, alcoholic beverages, and caffeine.

Toxicant-induced Loss of Tolerance (TILT) involves:

- Initiating toxic exposure(s)
- Fundamental breakdown in innate tolerance
- Adverse and amplified responses to previously tolerated and structurally diverse exposures including common chemicals, foods, drugs, alcoholic beverages, caffeine, and tobacco smoke

Evidence for Toxicant-induced Loss of Tolerance

“Our results suggest that serious and multiple dysfunctions of chemical defensive system found in these patients may mainly not depend on genetic defects, but instead may rely on non-genetic modifications of metabolizing/antioxidant enzyme expression and/or activity…."

(De Luca et al. 2010)

e.g., epigenetic changes

How are chemical intolerances and autism alike?

<table>
<thead>
<tr>
<th>Symptoms/Intolerances</th>
<th>CI</th>
<th>Autism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multisystem symptoms, especially neurocognitive, mood, GI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Can be initiated by pesticides and other toxicants</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Food intolerances</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Food cravings</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemical intolerances</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Drug allergies/adverse drug reactions</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Chemical Intolerance and Autism Study

Are mothers of children with autism and/or AD/HD more chemically intolerant than mothers of neurotypical children?

National online survey >600 mothers
AD/HD: professional diagnosis, DSM criteria
Autism: parental report of professional diagnosis
Mothers of children with Autism (n=282), ADHD (n=258) and Controls (n=93)

Chemical Intolerance vs. Autism

• Exposures in chemically susceptible adults may lead to Toxicant-induced Loss of Tolerance (TILT)
• Exposures in utero or in children affect their developing nervous, immune, and endocrine systems causing permanent changes.
Specific effects may depend on:
1. Nature of chemicals
2. Timing of exposure
3. Dose
4. Susceptibility of the individual

Chemicals Associated with Autism

Top 10
- Lead
- Methylmercury
- PCBs
- Organophosphate pesticides
- Organochlorine pesticides
- Endocrine disruptors
- Automotive exhaust
- Polycyclic aromatic hydrocarbons
- Brominated flame retardants
- Perfluorinated compounds

A Comparative Study of Pesticide Use in Homes of Pregnant Women Living at the Texas-Mexico Border and in New York City
Beatriz Tapia, Patsy G. Bortoni, Enrique Escobedo, David Camann, Lynne P. Heilbrun, Robin M. Whyatt, Claudia S. Miller

Used air monitoring equipment to measure:
- Organophosphates
- Synthetic Pyrethroids
- Organochlorines
- Carbamates
- Fungicides
- Herbicides

Pesticide comparison: New York City vs. South Texas

Study Population:
25 Pregnant Hispanic Women 18-35 y/o, 30-34 weeks gestation, recruited from maternity clinics in Hidalgo County

Inclusion criteria:
• Stable residency within drivable distance
• Non smoker/no illicit drugs/moderate drinker
• No major health problems (DM, AHT, HIV, NS)
• Homemakers who spend majority day in home
Pesticide Exposure in South Texas

Methods:
- Questionnaire covering demographics, home characteristics, residential history, and lifestyle
- Installation of PUF sampler in home
- Two weeks later - follow-up questionnaire
- All samples (air and dust) sent for analysis

Pesticides analyzed in home air and dust (~45 total)

- Organophosphates
  - Azinphos-methyl
  - Chlorpyrifos
  - Diazinon
  - Ethyl Parathion
  - Malathion
  - Methyl parathion
  - Propetamophos
- Carbamates
  - Bendiocarb
  - Carbaryl
  - Carbosulfan
  - Fenoxycarb (also IGR)
- Synthetics
  - MGK 264
  - Piperonyl butoxide

Fungicides
- Captan
- Synthetic Pyrethroids
  - Bioallethrin
  - Bifenthrin
  - Cis-permethrin
  - Cyfluthrin
  - Cypermethrin
  - Deltamethrin
  - Gamma-cyhalothrin
  - Lambda-cyhalothrin
  - Prallethrin
  - Sumithrin
  - Tetramethrin
  - Trans-permethrin

Insect Growth Retardant (IGR)
- Fenoxycarb (also carbamate)
- Hydroprene
- Methoprene

Organochlorines
- 4,4'-DDD
- 4,4'-DDE
- 4,4'-DDT
- Alpha-chlordane
- Dieldrin
- Gamma-chlordane
- Heptachlor
- Lindane

Herbicides
- Altrazine
- Metolachlor
- Pendimethalin
- Simazine
- Trifluralin

Others
- Fipronil
- Ortho-phenylenediamine
- Sulfuramid

Results:
- 68% of these households reported pesticide use vs. 85% of previously studied NYC households
- 35% used two or more pest control methods
- 14 pesticides detected including several organophosphates: ortho-phenylenediamine in 92% of home air samples, followed by chlorpyrifos in 80%, propoxur in 76%, diazinon in 72%, and trifluralin in 60%

Pesticide Exposure in South Texas

Conclusions
Result cont.
- Household pesticide exposures during pregnancy in South Texas were similar to those in NYC
- In both Hidalgo County and NYC, the principal reason for organophosphate pesticide use were roaches
- Offspring of mothers exposed in NYC showed significant neurodevelopmental problems
- Neurodevelopmental studies among South Texas children exposed to pesticides are lacking
Case Study

- 36 year old woman with no prior problems
- Exposed to Dursban (Chlorpyrifos) in 2000
- TILT
- Multiple system symptoms
- Child with AD/HD
- Child with PDD/NOS
- History of extermination services > 10 years

Pesticide Sampling

- Tested foam cushions in homes treated with pesticides
- Dust samples from window sills, over under refrigerator, door thresholds, 24 hour air samples

(Pamann et al., 2011)

Persistence of Pesticides in Homes

<table>
<thead>
<tr>
<th>Indoor Air ng/m³</th>
<th>Chair Cushion (μg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outer</td>
</tr>
<tr>
<td>2004</td>
<td>6.8</td>
</tr>
<tr>
<td>2010</td>
<td>2.78</td>
</tr>
</tbody>
</table>

Pesticide levels in dust and air were highly correlated in the 2 homes

Half-life Chlorpyrifos: 4.5 – 6 years

Persistence of Pesticides in Residential Indoor Air and Chair Seat Foam  Camann DE, You A, Hedin LP, Walker T, Miller CS. (Indoor Air 2011 Conference)

Mercury in Texas related to autism rates

Environmental mercury release, special education rates, and autism disorder: an ecological study of Texas

Raymond F. Palmer *, Steven Blanchard *, Zachary Stein *, David Mandell, Claudia Miller *

Results: For every 100 pounds of Hg Release There is a 2% increase in autism rates

Where has it changed over time?

Rates of Autism Growth by TEA Regions:
- Highest Growth Quartile
- Lowest Growth Quartile
Mercury: a ubiquitous neurotoxin in food, air, water, and medicine

The mercury cycle

What we know about BIOLOGY: Involves impairment in multiple systems.

Genes AND Environment

Various environmental triggers interact with various susceptible genotypes.

Genes: Individual susceptibility, one size doesn’t fit all.

Autism is a Complex Set of Disorders

Multiple genes are involved in conferring autism susceptibility

Exposures

Biological Systems

Systems Biology

Prevention efforts through understanding G x E
Exposure of the U.S. population to toxic environmental chemicals has increased over the last 20 years.

Human exposure to ubiquitous neurotoxins affects women of child bearing age and their infants.

The developing fetus is exquisitely vulnerable to pharmaceutical products and other environmental chemical exposures that come from food, air, water, and medicine.

Ubiquitous Environment Exposures (neurotoxins and/or endocrine and immune disruptors) associated with ASD:
- Air Pollution
- Various Medicines
- Pesticides
- Plastics, Vinyl, Flame retardants
- Heavy metals
- Where you live makes a difference

Broad literature on the adverse consequences of environmental pollutants effecting childhood development

Food-Air-Water-Medicine

Individual susceptibility

How do you measure Environmental exposure?

- Comprehensive Survey?
  - Recall bias or not knowing
- Blood, hair, urine, nails?
  - Can only reveal relatively recent exposure
- Home air samples?
- Foam biopsies from furniture cushions, teddy bears, mattress from the house of conception

Submitted to state-of-the-art Mass Spectrometry methods

None of these samples can reliably capture exposure during critical windows of neurodevelopment in the womb or shortly after birth.

Results

- Acetaminophen, pesticides, plastics, and essential fatty acids in deciduous molars: potential biomarkers of perinatal exposure.
  
  
  Autism Speaks 2013 Trail Blazer award: 71 ASD teeth analyzed

- Exploring other chemicals stored in baby teeth.

Significance:

- None of the chemicals we detected have previously been detected in human teeth.
- Preponderance of organic chemicals measured in teeth appear to represent perinatal uptake during crown formation, but some small fraction likely reflects later childhood uptake after crown formation.
### Research Question:

Is autism among the Hispanic population insufficiently understood?

To investigate environmental and genetic factors

### Study Population
- 20 cases and their biological mother
- 20 controls
- Mexican-American ethnicity, child between the ages of 2—21 (recent change), living with biological mother, English speaking

### Residing in the study catchment areas
- Hidalgo and Cameron counties
- Or no more than a 2-hour drive assessment sites

### Methods
- Pre-screening – phone interview
- Three clinic visits:
  - Obtain consent, master questionnaire, diagnostician evaluations, and biosamples collection
  - Travel stipend and completion of study compensation

### U.S Hispanic Research Center (HARC)- A Pilot Study

<table>
<thead>
<tr>
<th>Polynsaturated fatty acids</th>
<th>No.</th>
<th>Teeth</th>
<th>Detections</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA, C18:2 n6, linoleic acid: source of all omega 6 fatty acids</td>
<td>71</td>
<td>71</td>
<td>100%</td>
</tr>
<tr>
<td>ALA, C18:3 n3, alpha-linolenic acid: source of all omega 3 fatty acids</td>
<td>71</td>
<td>15</td>
<td>21%</td>
</tr>
<tr>
<td>ARA, C20:4 n6, arachidonic acid: omega 6</td>
<td>71</td>
<td>60</td>
<td>85%</td>
</tr>
<tr>
<td>DHA, C22:6 n3, docosahexaenoic acid: omega 3</td>
<td>71</td>
<td>14</td>
<td>20%</td>
</tr>
</tbody>
</table>

LA and ALA are primarily derived from plants, while ARA and DHA come from animals. ARA deficiency can lead to growth problems and infections, while too much DHA can contribute to cardiovascular issues.
Biosamples to be Collected

- Blood Samples (Mother and Child)
  - Testing for:
    - Immunology
    - Genetics
- Hair (Child Only)
  - Heavy metals
- Saliva (Mother and Child)
  - Genetics
- Deciduous Teeth (Child Only)
  - Heavy metals
  - Medication, pesticides and other chemicals
- Urine (Child Only)
  - Pesticides

Expected Outcomes and Implications

- Demonstrate feasibility of U.S Hispanic Autism Research Center (HARC) in South Texas
- Shed light into significant differences in autism in Hispanic children and possible lack of diagnosis
- Identify specific challenges faced by families that have children with autism in the Lower Rio Grande Valley (LRGV)
- Become a resource of LRGV

South Texas Autism Research (STAR): Autism Tooth Fairy Study

Mission: To investigate gene/environment interactions as risk factors for the prevention of Autism Spectrum Disorders

Currently seeking funding

Phase 1: to compare chemical concentrations between typically developing children and those with Developmental Disabilities.

Phase 2: understand what kind of individual genetic susceptibilities to specific chemical exposures lead to Developmental Disabilities.

It takes a village

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