

Environmental Factors in the Etiology of Autism

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What do we mean by "environment?"

- Everything that is not inherited through our DNA
- Focus particularly on factors that are amenable to change:
 - At the individual or societal level

Vulnerability of Children

- Critical windows in prenatal and early postnatal life when disruption of normal developmental processes may cause irreparable damage
- Immune, endocrine, & nervous systems continue to develop for years – and each can influence the other
- Metabolizing enzymes differ
- Studying adult neurological status not adequate for predicting effects during phases of brain development
- New evidence adult immune system not representative of early life vulnerability (Dietert & Piepenbrink 2005)
- Effects from prenatal exposures may manifest long afterwards (Diethylstilbestrol & vaginal carcinoma)

Increased Exposures to Children

- Children spend time on the floor – sitting, crawling
- Hand-mouth behaviors imply greater ingestion of vast array of contaminants
- Exposures through inhalation higher per unit body weight: increased surface area for volume of inhalation
- Exposures through ingestion higher per unit body weight: fluid intake greater
- Breast-milk as vector, esp lipophilic compounds like organochlorines, brominated flame retardants

Cognitive Developmental Toxins

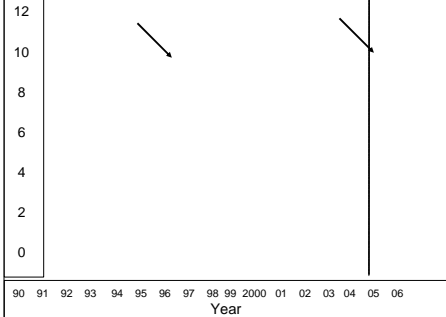
- Lead
- Radiation
- PCBs
- Mercury
- Organophosphate pesticides
- Infections
- Tobacco

Time trends

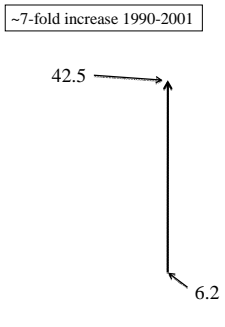
- Is the incidence of autism:
 still rising?
 plateauing?
 declining?

California Dept of Developmental Services Quarterly Population Incidence Rates

Quarterly number of new cases
per 10,000 Children



Cumulative Incidence by Birth Cohort



Hertz-Picciotto & Delwiche 2009

What does it mean?

- Rise in numbers receiving services
- Could be due to:
 - Increased awareness
 - Earlier age at diagnosis
 - Better diagnosis -- changes in definitions
 - Inclusion of milder cases
 - More funding available
 - Greater sense of hopefulness about treatment
 - True increase in incidence

How much of the 600% increase could have resulted from:

- Change in DSM criteria: 120%
 - Trend towards younger age at diagnosis: 24%
 - Broadening to include milder cases: 56%
-
- Total (from these 3): 200%

Hertz-Picciotto & Delwiche 2009

Comments

- Results not affected by migration
- DDS data collection methods relatively constant over last 18 years
- Good statewide coverage
- First attempt to quantify several artifactual contributions to the rise in autism
- DDS data not complete
- Difficult to measure awareness

Time Trends

- asthma, obesity, ADHD, diabetes, and mental health disorders (OCD, bipolar)

Is there a common set of environmental exposures that provides a unifying explanation for the increases in these conditions in recent decades?

How would one answer this question?
The people who study these diverse outcomes do not ordinarily collaborate!!!

Correlates and causes of autism

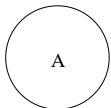
- Perspective
- Introduction to the CHARGE Study
- Results
- Future Directions

Facts about Autism

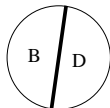
- Male:female ratio is 4:1
- Current reliable prevalence estimates in U.S.:
1 in 110 (=90 per 10,000)
- Strong genetic component
- Wide variation in severity
- Historically attributed to 'bad parenting'
- Neurobiologic basis: aberrant brain development
 - Post-mortem autopsy, electrophysiologic, MRI and fMRI
 - Highly diffuse throughout the brain
 - Early insult

Autism Causation is Multifactorial

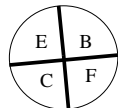
= multiple causes...
across the population and within an individual



Most rare:
one cause



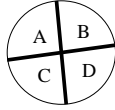
Possible: 2 causes



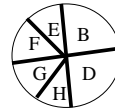
Most common: 3
or more causes

Genes & Environment in Autism

- Genetics: ~60-90% (twin studies) (*Rutter*)
- Environment: 10-40% = minimum
- Sum not 100%



- Risk Ratios of >10:
 - Congenital rubella (*Chess et al 1979*)
 - Thalidomide (*Rodier et al*)
- Risk Ratios ~2 to 5:
 - Maternal age (*Durkin et al 2008; Shelton et al. 2010*)
 - Male sex (*Fombonne 2003*)



What are the environmental factors contributing to autism?

- Environmental chemicals ?
- Microbiological agents ?
- Vitamin, nutritional deficiencies ?
- Gestational and perinatal conditions ?
- Medications ?
- Fertility treatments ?
- Medical interventions ?
- Modern technology ?

Mechanisms for Environmental Chemicals to Affect Autism Risk

- Direct action on neural tissue during:
 - Differentiation
 - Migration
 - Dendritic branching/pruning
 - Mini-column organization
 - Synaptogenesis
 - Myelination
- Effects on genes (e.g., epigenetic changes) that regulate CNS development
- Perturbation of immune signaling as a mediator of neuronal activity
- Disruption of basic cellular processes – mitochondria, or cell membrane
- Endocrine disruption: sex steroids or thyroid hormones



The CHARGE* Study

*Childhood Autism Risk from Genetics and the Environment



Goals of the CHARGE Study

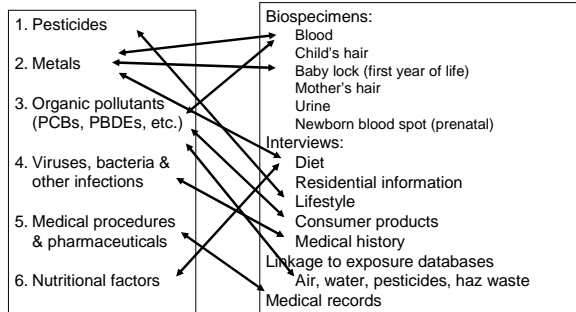
To identify causes and contributing factors to autism:

- Genetic susceptibility
- Environmental exposures
- Interactions of the two

To identify characteristics representing possible distinct etiologies for autism

- Immunologic
- Genetic/Genomic
- Metabolic/metabolomic
 - Phenotypic

Environmental Exposures & Ways to Assess





Eligibility Criteria

for all three groups:

- 24-60 months of age
- born in California in our catchment area
- whose parents speak English and/or Spanish
- living with at least one biologic parent



Data Collection:

- Child assessed at UC Davis M.I.N.D. Clinic:
 - Assessment for autism: ADOS & ADI-R
 - Tests of cognitive/adaptive development: Mullen's, Vineland
 - Medical exam & med history
- Parent completes forms
- Telephone interview conducted





Environmental Exposure Questionnaire :


- Socio-demographics
- Maternal reproductive Hx, medical conditions & medication use
- Selected dietary factors & supplement use
- Household products, including pesticides, metals
- Residential & occupational Hx's
- Lifestyle

Exposures, events, activities
covering prenatal, early childhood periods

CHARGE

Data Collection (con't):

- Specimens collected from family members:
 - blood
 - urine
 - hair
- Permission to obtain medical charts:
 - prenatal
 - labor and delivery
 - pediatrician



CHARGE

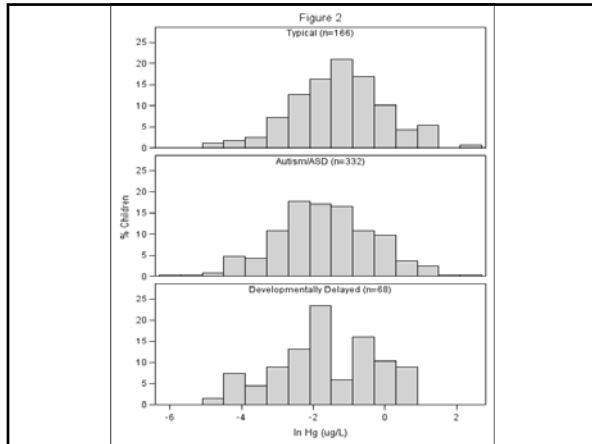
CHARGE STUDY RESULTS

1. Metals

CHARGE

Goal

- To determine whether current blood Hg levels differ in children with autism or ASD as compared with typically developing children



Proportions exposed by case status

	Autism/A SD N=249	Dev Delay (DD) N=60	Typical Dev (TD) N=143
Ate any fish	(43%)	68%	(76%)
Dental amalgams and chew or grind teeth	1.5%	2.4%	1.9%
Thimerosal-containing vaccine in last 90 days	3%	8%	5%
Nasal spray or earwax removal	19%	23%	13%

Influences on Blood Hg*

	<u>Change in blood Hg</u>	<u>P-value</u>
Autism or ASD	+ 4%	0.75
Developmental delay (DD)	- 44%	0.03
Ate tuna (1+ servings/wk)	+ 82%	<0.0001
Ate ocean fish (1+ servings/wk)	+ 70%	<0.0001
Ate freshwater fish (1+ serv./wk)	+101%	0.0006
Hg amalgams x chew/grind teeth	+ 19%	0.005
Nasal spray or ear wax removal	+ 17%	0.33

* Adjusted for child's age and sex; mother's education and birthplace

Hertz-Picciotto et al Environ Health Persp 2009


Conclusions: Hg – current blood

- Children with ASD have reduced blood Hg concentrations, as compared with TD children
- This was due to lower consumption of fish.
- After adjustment for Hg sources, children with ASD do not differ from TD children in their blood Hg concentrations

Children with ASD do not have higher blood Hg.

Does not address question of Hg as a causal factor.

Hertz-Picciotto et al Environ Health Persp 2009

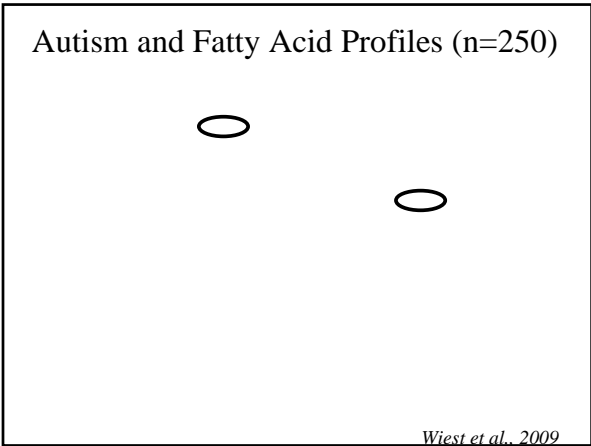


CHARGE STUDY RESULTS

1. Metals
2. **Nutritional Factors**

Goal:

- To determine whether lipid profiles distinguish children with vs. without autism



CHARGE Autism and Fatty Acid Profiles

Docosahexanoic acid (DHA)

- abundant in phospholipids of brain and retina
- contributes to membrane structure and function

Other Functions:

- Inhibition of neuronal apoptosis and
- Regulating neuronal excitability through GABA receptors

Developing brains obtain DHA from circulation

Wiest et al., 2009

CHARGE **CHARGE STUDY RESULTS**

1. Metals
2. Nutritional factors
3. **Household products: pesticides**

Background: Pesticides

- Often designed to target CNS of insects, rodents or other species.
- Two previous studies linked prenatal pesticide exposures to higher risk of autism or PDD symptoms (*Roberts et al 2007, Eskenazi et al 2007*)
- Neither looked at household pesticides
- Neither used ADOS or ADI-confirmed cases

CHARGE

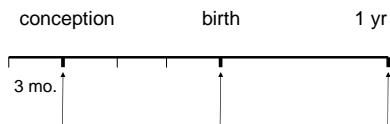
Goal

- To determine whether household pesticide use during pre-conception, gestation, or the first year of life is associated with higher risk for a confirmed autism diagnosis.

CHARGE

Data Collection: Use of Pesticides and Other Home Products

- Questions in telephone interview
- Included sprays, pet pest soaps & shampoos, foggers, & professional services
- For each product, the mother was asked about timing of use:





U.S. Population Exposures to Pyrethroid Pesticides

- NHANES of 1999-2002:
- Measurable levels of 3-phenoxybenzoic acid (3PBA) were found in 75% of urine samples analyzed for pesticides ($n = 3,048$) (CDC 2005)
- 3PBA is a metabolite of several commonly used pyrethroids, including:
 - permethrin
 - cypermethrin
 - cyhalothrin
 - deltamethrin
 - fenvalerate.

→ Exposures are widespread

Significance of the CHARGE Study

- Largest & most comprehensive study yet of environmental factors in autism
- Close to 1400 children and their families enrolled
- Most other studies of the environment have relied on 'ecologic design' – no individual level data
- Confirmation of diagnoses
- Population-based
- Link to state-of-the-art laboratories
- Biggest limitation is retrospective collection of data

Our focus is on modifiable risk and protective factors
- goal is to intervene and prevent autism!

MARBLES

Markers of Autism Risk in Babies—Learning Early Signs



A study of pregnant moms, who already have a child with autism, following their pregnancies and new child

Next steps

- Maternal nutritional factors
- Air pollution
- Mercury in baby hair & newborn blood spots
- Household exposures
flame retardants, plastics
- Maternal acute and chronic medical conditions
- Medical interventions
- Gene x environment interactions
- Gene x nutrient interactions

Investigators & Collaborators

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Be in **CHARGE** !



<http://beincharge.ucdavis.edu/>

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End

Thank you!
