Autism and Our Planet: The Significance of Environmental Toxicology in Neurodevelopment

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ABSTRACT

The Center For Disease Control has announced that autism is the fastest growing developmental disability in the United States. This rapid increase in diagnoses suggest the involvement of environmental factors.

Dr. Chapman will discuss current research and statistics implicating environmental toxicants, in combination with genetic factors, and their effect on neurodevelopment.

She will also discuss steps our healthcare system needs to take to reduce childhood exposures and risk.

Rethinking Autism

Where is autism?

Brain-based **vs.** Systemic

What is the plasticity of the disease?

Hardwired and fixed **vs.** Flexible and modifiable

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Rethinking Autism

What is the cause of autism?

Genetics ***vs.*** Genetic susceptibilities and environmental insults

When does autism begin?

Prenatal pathology ***vs.*** Prenatal *and* post natal triggers affecting course of disease

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Rethinking Autism

Autism as a behavioral diagnosis

VS

Autism as a complex multi-system metabolic disorder that can be treated not only with behavioral therapies and psychiatric medications but also functional physical evaluation and biological therapies

Rethinking Autism

"Autism: a brain disorder or a disorder that affects the brain?"

Martha Herbert, MD

Clinical Neuropsychiatry 2005; 2(6):354-79.

The brain is downstream of the body

If the body suffers an inflammatory condition, metabolic disorder, gastrointestinal disease, nutritional deficiency, toxic insult or oxidative burden, the brain is deeply affected.

Environmental toxins are only one piece of the puzzle!

Sensory Integration issues
Immunological dysfunction
Allergy /Atopy
Neurological Vulnerability
Nutritional deficiency
Metabolic dysfunction
Gastrointestinal illness
Neurological concerns
Genetic issues
Viral/ infectious
Toxic influence

EPA Builds List of Potentially Dangerous Chemicals

- As the rates of learning disabilities, autism and related conditions rise, the Environmental Protection Agency is preparing to release a roster of the pollutants likely to contribute to these or other neurological disorders.

December 2010

List of Implicated Toxicants

- 2-ethoxyethyl Acetate – a solvent, used as a coating for wood, metal and other materials; sometimes found in cosmetics.
- Acibenzolar-S methyl -- a fungicide
- Acrylamide – a chemical that is produced naturally in certain foods when they are cooked at high temperatures. It is also manufactured industrially for use in the production of polyacrylamide gels, which are used for various purposes, including the treatment of drinking water and wastewater; and found in cigarette smoke.
- Aldicarb – a pesticide
- Allethrin – a pesticide
- Aluminum (lactate) -- used in lotions to treat very dry skin.
- Aminopterin – chemical originally developed for use in cancer treatment;
- Arsenic -- a semi-metal element, which enters drinking water supplies from natural deposits in the Earth or from agricultural and industrial practices.
- Aspartame – an artificial sweetener
- Benomyl – a fungicide
- Benzene – a volatile organic chemical, formed through natural processes, such as volcanoes and forest fires. It is also formed from industrial processes, and is used to make plastics, rubber, resins and synthetic fabrics like nylon and polyester. Benzene is also a natural part of crude oil, gasoline and cigarette smoke.
- Bioallethrin (s-bioallethrin) – a pesticide
- Bis(tri-n-butyltin)oxide – a biocide
- Bisphenol A – This chemical is the main ingredient in polycarbonate plastic, used to make water bottles, baby bottles and food storage and heating trays; and epoxy resin, which is used in the lining of most food and beverage cans.
- Butylated Hydroxy Anisole – a food additive, better known as BHA.

- Butylated hydroxytoluene – a toluene-based ingredient used as a preservative in food and personal care products.
- Cadmium – a natural element in the Earth's crust. It is found in food, and people can be exposed from smoking cigarettes or breathing cigarette smoke or from water or industrial facilities which release it into the air.
- Carbaryl -- insecticide
- Carbon monoxide -- an odorless and colorless toxic gas
- Chlordecone – an insecticide.
- Chlorine dioxide – a chemical mostly used to disinfect water.
- Chlorpyrifos -- insecticide
- Cypermethrin --insecticide
- DEET – a common ingredient in insect repellents
- Deltamethrin -- insecticide
- Diazinon – a pesticide
- Dieldrin – an insecticide no longer produced in the U.S., but still found in the environment.
- Ethanol – grain alcohol, produced from crops such as corn, used as a fuel additive, solvent and for other purposes.
- Ethylene thiourea – an industrial chemical mostly used to make rubber products, but also in the manufacture of fungicides and rodenticides.
- Fluazinam – a fungicide
- Heptachlor – a non-agricultural insecticide, whose use is now very limited.
- Hexachlorobenzene – can be formed as a byproduct during the manufacture of chemicals used as solvents, other chlorine-containing compounds, and pesticides. Small amounts of hexachlorobenzene can also be produced during combustion processes such as burning of city wastes. Currently, the substance is not used commercially in the United States.
- Hexachlorophene – a disinfectant.
- Lead – This heavy metal occurs naturally in the Earth's crust. It was formerly used as a gasoline additive and was also commonly added to paint. Lead pipes may also contaminate drinking water. Currently, coal-fired power plants and other industrial uses release lead particles into the air.

- Lindane – a chemical used to treat scabies and lice.
- Maneb – a fungicide
- Methanol – also known as wood alcohol, an alternative fuel, and other uses
- Methylparathion – a pesticide
- Monosodium Glutamate – a flavor enhancer, used as a food additive
- Nicotine – the addictive drug in tobacco
- Methoxyethanol, 2 – an organic compound used mainly as a solvent
- Methylmercury — a form of mercury found in contaminated fresh water and salt water fish. It gets into the air when coal, oil or wood are burned as fuel, or when mercury-contaminated wastes are incinerated.
- Ozone – a gas that occurs both in the Earth's upper atmosphere and at ground level
- Paraquat – an herbicide.
- Parathion (ethyl) – an insecticide
- PBDEs – Polybrominated diphenyl ethers, called PBDEs, are used as flame retardants, among other purposes. Some types of PBDEs have been banned, or phased out, but industry has developed others to replace them.
- PCBs (generic) – Polychlorinated biphenyls (PCBs) are a group of chemicals that were used as insulation in electrical transformers, and for other industrial purposes. They are no longer manufactured, but have persisted in the environment.
- Permethrin – an insecticide
- Phthalate, di-(2-ethylhexyl) – This phthalate, commonly referred to as DEHP, is found in many plastic products.
- Tebuconazole – a fungicide
- Toluene – a common solvent, found in many consumer goods, including floor polish, moisturizing cream, lubricating oils, paint thinners.
- Tributyltin chloride – Manmade organic substances containing the metal tin. They are used as pesticides and biocides in marine antifouling paints and in wood preservatives.
- Trichlorfon – an insecticide
- Trichloroethylene – used as a solvent to clean metal parts and for other industrial processes, often found as a water contaminant.

In Utero Exposures and Autism

- **The only in prenatal exposure well documented is Valproic acid**
- **All contaminants are not equal!**
  - Organohalogens higher in mom than baby
  - PCBs higher in baby than mom
  - Mercury is high/ uniform in all matrices
- **National Children's Study:** www.nationalchildrensstudy.gov

- Larry L. Needham†, Philippe Grandjean*†§, Birger Heinzow, Poul J. Jørgensen¶, Flemming Nielsen‡, Donald G. Patterson, Jr.†, Andreas Sjödin†, Wayman E. Turner†, and Pal Weihe. **Partition of Environmental Chemicals between Maternal and Fetal Blood and Tissues.** Environ. Sci. Technol., Article ASAP Publication Date (Web): December 17, 2010
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PDBEs: Halt Flames *and* Neurodevelopment!

Cord Blood PDBE levels have neurodevelopmental consequences!

- Samples taken from 329 mothers and children in Manhattan who delivered in proximity to the 9/11/2001 attack

Julie B. Herbstman, Andreas Sjödin, Matthew Kurzon, Sally A. Lederman, Richard S. Jones, Virginia Rauh, Larry L. Needham, Deliang Tang, Megan Niedzwiecki, Richard Y. Wang, and Frederica Perera. **Prenatal Exposure to PBDEs and Neurodevelopment** Environmental Health Perspectives. 2010;118(5):712-719.

Autism and Heavy Metals

Children with higher levels of heavy metals in their urine have more severe symptoms of autism!

- Adams, JB, M Baral, E Geis, J Mitchell, J Ingram, A Hensley, I Zappia, S Newmark, E Gehn, RA Rubin, K Mitchell, J Bradstreet, and JM El-Dahr. 2009. **The severity of autism is associated with toxic metal body burden and red blood cell glutathioine levels**. Journal of Toxicology doi:10.1155/2009/532640

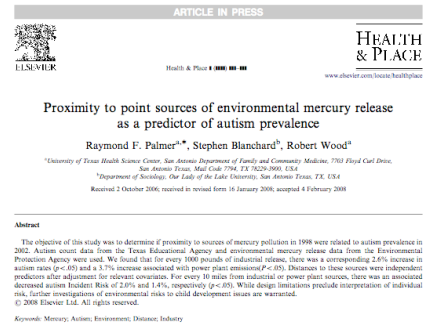
The "V" Word

- www.vaccinesafety.edu/components.htm

- **CDC 2001:** Except for influenza, thimerosal is removed from, or reduced in, all vaccines routinely recommended for children 6 years of age and under manufactured for the U.S. market.
- Main Preservative: 2-phenoxyethanol
- ***Aluminum: used as an adjuvant***

- Bishop N J; Morley R; Day J P; Lucas A (1997) **Aluminum neurotoxicity in preterm infants receiving intravenous-feeding solutions**. The New England journal of medicine. 336(22):1557-61.

- Aluminum exposure in the first six months of life:
- 4mg from vaccines
- 10mg from breast milk
- 40mg from dairy infant formula
- 125 mg from soy based infant formula
- **www.vaccine.chop.edu**



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Proximity to point sources of environmental mercury release as a predictor of autism prevalence

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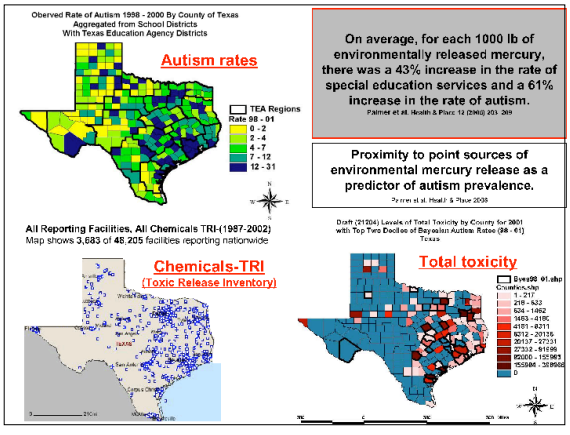
Abstract

The objective of this study was to determine if proximity to sources of mercury pollution in 1998 were related to autism prevalence in 2002. Autism count data from the Texas Educational Agency and environmental mercury release data from the Environmental Protection Agency were used. We found that for every 1000 pounds of industrial release, there was a corresponding 2.6% increase in autism rates ($p<.05$) and a 3.7% increase associated with power plant emissions($P<.05$). Distances to these sources were independent predictors after adjustment for relevant covariates. For every 10 miles from industrial or power plant sources, there was an associated decreased autism Incident Risk of 2.0% and 1.4%, respectively ($p<.05$). While design limitations preclude interpretation of individual risk, further investigations of environmental risks to child development issues are warranted.

Keywords: Mercury; Autism; Environment; Distance; Industry



Childhood Lead Exposure

- Current CDC standard is that lead level <10 µg/dL "does not define a threshold for the harmful effects of lead"
- Current reccomendations are to provide education on avoidance and screen for anemia when elevated levels are found
- Treatment is not rendered for kids until BLL is >45
- Lanphear BP, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect. 2005 Jul;113(7):894-9.

Why heavy metals in Autism?

Direct Exposure- lead, mercury, aluminum or arsenic can sometimes be implicated

Faulty Genetics- Epigenetic differences can lead to sluggish biotransforamation/detoxification and metabolic storage

- Walsh, W.J., Usman, A., and Tarpey, J.; Disordered Metal Metabolism In a Large Autism Population, Proceedings of the Amer. Psych. Assn.; New Research: Abstract NR109, New Orleans, May, 2001.
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Environment and Genetics

- **Environmental toxicants interfere with faulty epigenetics and the end result is oxidative stress and neuroinflammation!**
- Herbert MR. **Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders**.Curr Opin Neurol. 2010 Apr;23(2):103-10
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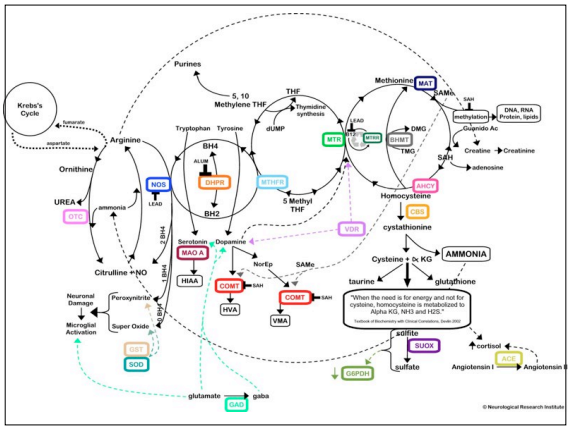


Enzyme SNP's Studied In Autism

- **MTHFR - Methylenetetrahydrofolate reductase**
  - Defective folate metabolism
  - Elevated homocysteine levels
  - Defective ability to methylate DNA
  - Global loss of methyl groups

James, S.J., Melnyk, S., Jernigan, S., Hubanks, A., Rose, S, & Gaylor, D.W. (2008). Abnormal Transmethylation/transsulfuration Metabolism and DNA Hypomethylation Among Parents of Children with Autism. *Journal of Autism and Devopmental Disorders*. Published online only July 11, 2008.

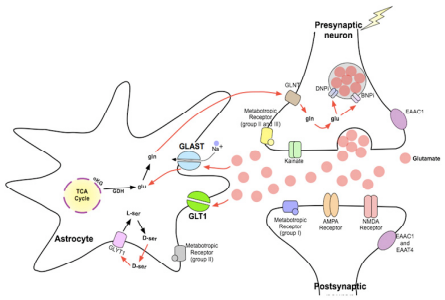
Enzyme SNP's Studied In Autism

- **CBS - Cystathionine Beta- Synthase**
  - Joins the methyl and sulfur pathways
  - This is a one-way reaction that permanently removes homocysteine from the methionine cycle and initiates the transsulfuration pathway for the synthesis of cysteine and glutathione
- **Glutathione-S-transferase**
  - Conjugate glutathione with toxins for Phase 2 biotransformation and elimination
- Williams TA. Mars AE. Buyske SG. Stenroos ES. Wang R. Factura-Santiago MF. Lambert GH. Johnson WG. Risk of autistic disorder in affected offspring of mothers with a glutathione S-transferase P1 haplotype. Archives of Pediatrics & Adolescent Medicine. 161(4):356-61, 2007 Apr.

How Do Heavy Metals Damage Neurons?

Two major mechanisms of action:

1. **Oxidative Damage**
2. **Neuroglial excitotoxicity/ inflammation**



Yu-Peng Liu1, Chung-Shi Yang2, Shun-Fen Tzeng1, A Possible Therapeutic Strategy for CNS Repair: To blockade calcium regulation of glutamate aspartate transporter regulation in astrocytes, Journal of Neurochemistry. 2008 Apr;105(1):137-150

Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism

Diana L. Vargas, MD,[1,2] Caterina Nascimbene, MD,[1–3] Chitra Krishnan, MHS,[1] Andrew W. Zimmerman, MD,[3,4] and Carlos A. Pardo, MD[1,2,5]

Autism is a neurodevelopmental disorder characterized by impaired communication and social interaction and may be accompanied by mental retardation and epilepsy. Its cause remains unknown, despite evidence that genetic, environmental, and immunological factors may play a role in its pathogenesis. To investigate whether immune-mediated mechanisms are involved in the pathogenesis of autism, we used immunocytochemistry, cytokine protein arrays, and enzyme-linked immunosorbent assays to study brain tissues and cerebrospinal fluid (CSF) from autistic patients and determined the magnitude of neuroglial and inflammatory reactions and their cytokine expression profiles. Brain tissues from cerebellum, midfrontal, and cingulate gyrus obtained at autopsy from 11 patients with autism were used for morphological studies. Fresh-frozen tissues available from seven patients and CSF from six living autistic patients were used for cytokine protein profiling. We demonstrate an active neuroinflammatory process in the cerebral cortex, white matter, and notably in cerebellum of autistic patients. Immunocytochemical studies showed marked activation of microglia and astroglia, and cytokine profiling indicated that macrophage chemoattractant protein (MCP)-1 and tumor growth factor-β1, derived from neuroglia, were the most prevalent cytokines in brain tissues. CSF showed a unique proinflammatory profile of cytokines, including a marked increase in MCP-1. Our findings indicate that innate neuroimmune reactions play a pathogenic role in an undefined proportion of autistic patients, suggesting that future therapies might involve modifying neuroglial responses in the brain.

Ann Neurol 2005;57:67–81

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Pathophysiology 13 (2006) 171–181

PATHOPHYSIOLOGY

Review

Oxidative stress in autism

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Abstract

Autism is a severe developmental disorder with poorly understood etiology. Oxidative stress in autism has been studied at the membrane level and also by measuring products of lipid peroxidation, detoxifying agents (such as glutathione), and antioxidants involved in the defense system against reactive oxygen species (ROS). Lipid peroxidation markers are elevated in autism, indicating that oxidative stress is increased in this disease. Levels of major antioxidant serum proteins, namely transferrin (iron-binding protein) and ceruloplasmin (copper-binding protein), are decreased in children with autism. There is a positive correlation between reduced levels of these proteins and loss of previously acquired language skills in children with autism. The alterations in ceruloplasmin and transferrin levels may lead to abnormal iron and copper metabolism in autism. The membrane phospholipids, the prime target of ROS, are also altered in autism. The levels of phosphatidylethanolamine (PE) are decreased, and phosphatidylserine (PS) levels are increased in the erythrocyte membrane of children with autism as compared to their unaffected siblings. Several studies have suggested alterations in the activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase in autism. Additionally, altered glutathione levels and homocysteine/methionine metabolism, increased inflammation, excitotoxicity, as well as mitochondrial and immune dysfunction have been suggested in autism. Furthermore, environmental and genetic factors may increase vulnerability to oxidative stress in autism. Taken together, these studies suggest increased oxidative stress in autism that may contribute to the development of this disease. A mechanism linking oxidative stress with membrane lipid abnormalities, inflammation, aberrant immune response, impaired energy metabolism and excitotoxicity, leading to clinical symptoms and pathogenesis of autism is proposed.

What should we do about it?

- Education and Awareness
- Limit Exposure
- Everyday detox
- Investigate toxic levels more thoroughly
- Treat more aggressively when toxicants are found

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