Biologic Plausibility of the Hypothesis that Autism is a Unique Type of Mercury Poisoning

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Presentation to the Institute of Medicine Immunization Safety Review Committee
Thimerosal-Containing Vaccines and Neurodevelopmental Outcomes

July 16, 2001
The Autism – Mercury Hypothesis


- In individuals with a genetic susceptibility (such as a defect in enzymes which are responsible for clearing toxic heavy metals), prenatal and early postnatal exposure to mercury leads to neurologic damage resulting in autistic symptoms.

- Hypothesis is supported by symptom comparisons, toxicity studies, case studies, and epidemiology.

- The hypothesized primary source of mercury is thimerosal or ethylmercury.
Potential Sources of Exposure

• For a fetus or infant, the main sources of exposure to mercury would be:
  – Maternal amalgams
  – Maternal fish consumption
  – Ear drops, saline nasal drops, OTC products
  – Vaccines
    • Rho-gam
      Rh- mothers: 3% general population, 12% Autistic children, 10% PDD-NOS (Juul-Dam 2001)
      Rh incompatibility associated with a high risk of developmental delays (Bolton 1997)
    • Influenza vaccine during pregnancy
      CDC recommends flu vax for all pregnant women who will be in the 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester during flu season (MMWR 7/13/01)
    • Childhood immunizations
      Thimerosal-containing DTaP still being distributed and sold in US as of 4/25/01 although no longer manufactured.
Biologic Plausibility

• The diagnostic traits of Autism/Autistic Spectrum Disorder (ASD) are found in cases of mercury poisoning (HgP).
• The diagnostic criteria of HgP are met in ASD.
• Much inter-individual variation in both disorders.

Diagnostic Criteria

<table>
<thead>
<tr>
<th>Autism</th>
<th>Mercury Poisoning</th>
</tr>
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<tbody>
<tr>
<td>Social deficits</td>
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Trait Comparisons

- Characteristics of ASD found in HgP cases and attributed to HgP by researchers.

Social Deficits

Language Deficits

Repetitive Behaviors

Sensory Abnormalities

ASD Defining Characteristics
Trait Comparisons – Core Characteristics of ASD also described in HgP Literature

Social Deficits
- shyness; social withdrawal;
- indifference to others;
- desire to be alone/aloofness;
- lack of facial expression

ASD Defining Characteristics

Language Deficits

Repetitive Behaviors

Sensory Abnormalities
Trait Comparisons – Core Characteristics of ASD also described in HgP Literature

Language Deficits
loss of speech or failure to develop speech; speech comprehension difficulties; articulation problems; verbalizing and word retrieval problems/word use and pragmatic errors; mild to profound hearing loss

ASD Defining Characteristics

Social Deficits

Repetitive Behaviors

Sensory Abnormalities
Trait Comparisons – Core Characteristics of ASD also described in HgP Literature

**Repetitive Behaviors**
- OCD traits, repetitive thoughts; circling, rocking, unusual postures; spontaneous dyskinesia/stereotypies - jerking/writhing movements, arm flapping, grimacing, akathisia/restlessness; perseveration

**ASD Defining Characteristics**
- Social Deficits
- Language Deficits
- Sensory Abnormalities
Trait Comparisons – Core Characteristics of ASD also described in HgP Literature

Sensory Abnormalities
abnormal sensation in mouth and extremities, astereognosis/stereognosis; touch aversion, over-under-sensitivity; photophobia; sound distortions; vestibular abnormalities

ASD Defining Characteristics

Social Deficits

Language Deficits

Repetitive Behaviors
Trait Comparisons
- Characteristics of ASD found in HgP cases and attributed to HgP by researchers.

Psychiatric Issues
Movement Disorder
Cognitive Impairments
Behavioral Problems

Associated Traits - ASD
Trait Comparisons – Associated Traits of ASD also described in HgP Literature

**Psychiatric Issues**
- depression, lack of initiative; anxiety;
- irrational fears; mood swings, aggression, irritability, anger, tantrums (children); anorexia

**Movement Disorder**

**Cognitive Impairments**

**Behavioral Problems**

**Associated Traits - ASD**
Trait Comparisons – Associated Traits of ASD also described in HgP Literature

**Cognitive Impairments**
- poor performance on language vs. performance IQ; attention deficits; short term, verbal, and auditory memory impairments; mental retardation/deterioration; executive function deficits; difficulty with multi-step commands; deficits in abstract thinking; impaired face recognition

**Psychiatric Issues**

**Movement Disorder**

**Behavioral Problems**

**Associated Traits - ASD**
Trait Comparisons – Associated Traits of ASD also described in HgP Literature

Movement Disorder
- difficulties sitting, crawling, standing, walking, & tendency to fall to one side (infants/toddlers);
- handwriting difficulties;
- limb apraxia/poor imitation;
- clumsiness;
- abnormal gait or posture

Psychiatric Issues

Cognitive Impairments

Associated Traits - ASD

Behavioral Problems
Trait Comparisons – Associated Traits of ASD also described in HgP Literature

**Behavioral Problems**
- hyperactivity; agitation;
- unprovoked crying (infants);
- self-injurious behavior - head banging and hand biting; toe walking;
- severe sleep problems; eating disorders

**Psychiatric Issues**

**Movement Disorder**

**Cognitive Impairments**

**Associated Traits - ASD**
Comparisons of Biological Abnormalities in ASD and HgP

<table>
<thead>
<tr>
<th>CNS - Structure</th>
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<tbody>
<tr>
<td>Neurochemistry</td>
</tr>
<tr>
<td>Neurophysiology</td>
</tr>
<tr>
<td>Autonomic disturbances</td>
</tr>
<tr>
<td>Biochemical</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Physical/Muscle Function</td>
</tr>
<tr>
<td>Immune System</td>
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</tbody>
</table>
## Biologic Abnormalities – Similarities between Hg and ASD

<table>
<thead>
<tr>
<th></th>
<th>Hg</th>
<th>ASD</th>
</tr>
</thead>
</table>
| **Biochemical**      | Blocks sulfate transporter  
                      Decreases glutathione  
                      Disrupts mitochondria | Low sulfate levels  
                      Low glutathione  
                      Mimics mitochondrial disorders |
| **Gastrointestinal** | Diarrhea/constipation/colitis  
                      Increased gut permeability  
                      Eating difficulties | Diarrhea/constipation/colitis  
                      Increased gut permeability  
                      Eating difficulties |
| **Physical/Muscle**  | Hyper/Hypo-tonia  
                      Poor muscle strength  
                      Cerebral palsy  
                      Oral motor problems  
                      Sweating, tachycardia  
                      Eczematous rashes | Hyper/Hypo-tonia  
                      Poor muscle strength  
                      Cerebral palsy incidence high  
                      Oral motor problems  
                      Sweating, tachycardia  
                      Eczematous rashes |
Sensitive groups

Variation in individual sensitivity to Hg (Hattis 1996)
- in adults: 78-fold
- in fetus/developing infant: approx. 10,000-fold

Elimination of mercury shows great variability in humans as well as animals. (Bartell 2000)
- Neonatal animals “more or less lack” the ability to excrete MeHg (Thuvander 1996)
- Younger, male mice eliminate MeHg poorly (Nielsen 1996)
- Milk diet increases GI absorption of metals (Kostial 1978)
- Gut bacteria essential to convert MeHg in bile to Hg2+; MeHg reabsorbed while Hg2+ excreted. (Wild 1997)
Sensitive Groups

Acrodyinia/Pink Disease: example of a sensitive group (Clarkson 1997)
- 1 in 500 exposed children affected
- Response occurring at low doses
- Painful “pink” hands and feet, peripheral neuropathy, sound/light sensitivity, apathy, aversion to touch, insomnia, rocking, hand rubbing, head-banging, poor muscle tone.

Autism
- 4:1 male:female ratio consistent with HgP
- Regression/delayed onset consistent with HgP
Immune system: Immunopathology

- Immune deficiency/dysfunction: defective or ineffective response.
- Hypersensitivity: overactive response, out of proportion to potential damage from the agent.
- Autoimmunity: inappropriate reaction towards self.
- Dysregulation of the immune system in children with autism leads to all three problems.
Th1 and Th2 balance of immune system

• Need both to work in balance; there should be feedback between them to maintain this. Autoimmunity may result from dysregulation of either side.

• Children with autism and those with Autistic Spectrum Disorders (ASD) are often shifted towards Th2 (allergy) and away from Th1 (viral/fungal killing). This leaves them predisposed to infections and to autoimmunity.

• Specific immune abnormalities have been found in 30-70% of patients with autism in a variety of studies. (Zimmerman 1999 and Heijnen 1997)
Immune Findings:

<table>
<thead>
<tr>
<th>Immune dysregulation</th>
<th>Hu 1999 and Bagenstose 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Th2 predominance</strong> with high IgE: mouse pups and MeHg</td>
<td>Thurvander 1996</td>
</tr>
<tr>
<td>High IgE in exposed workers</td>
<td>Dantas 1997</td>
</tr>
<tr>
<td>Increased reactivity to <strong>foods</strong>: IgE and IgG antibodies made after a single oral dose of Hg</td>
<td>Watzl 1999</td>
</tr>
<tr>
<td>Increased permeability of intestinal epithelium</td>
<td>Watzl 1999</td>
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**ASD**

<table>
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<tr>
<th>Immune dysregulation common predisposes to viral/fungal infections</th>
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<tr>
<td><strong>Th2 predominance</strong> with decrease in Th1 cytokines</td>
</tr>
<tr>
<td>Increased IgE in 68%</td>
</tr>
<tr>
<td>Increased reactivity to <strong>foods</strong>: IgE, IgA, IgG Abs in high amounts</td>
</tr>
<tr>
<td>T cell reactivity to food in 75%</td>
</tr>
<tr>
<td>Increased permeability of intestines</td>
</tr>
<tr>
<td>D’Eufemia 1996</td>
</tr>
<tr>
<td>Hg</td>
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<tr>
<td>------------------------------------------------------------------</td>
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<tr>
<td>Immune Findings:</td>
</tr>
<tr>
<td><strong>Hg</strong></td>
</tr>
<tr>
<td>Alters CD95-mediated <em>apoptosis</em>: small amounts of Hg cause human T cells to undergo apoptosis</td>
</tr>
<tr>
<td>Shenker 1998</td>
</tr>
<tr>
<td><strong>Decreases Natural Killer (NK) cells:</strong></td>
</tr>
<tr>
<td>Prenatal and/or postnatal exposure to MeHg in rat pups resulted in 57% decrease in NK cell activity. Wild 1997</td>
</tr>
<tr>
<td>MeHg exposure in adult mice resulted in 44% decrease in NK cell activity. Ilback 1991</td>
</tr>
<tr>
<td><strong>Increases chronicity of viral infections:</strong></td>
</tr>
<tr>
<td>MeHg in mice enhances viral virulence Koller 1975</td>
</tr>
<tr>
<td>and viral persistence Ilback 1996</td>
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### Autoimmunity: anti-brain antibodies

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<tr>
<td>Multiple types of <strong>serum anti-brain antibodies</strong> found in rats exposed to MeHg and in humans with Hg0. Rats develop anti-MBP, Anti-NAFP and anti-GFAP El-Fawal 1996</td>
<td>Many kinds of <strong>serum anti-brain antibodies</strong> found:</td>
</tr>
<tr>
<td>Brain antibodies are a biomarker of the effect of mercury rather than of exposure. Multiple high-titer anti-brain Abs (to MBP, NAFP, GFAP) correlated with the degree of subclinical sensorimotor deficits in workers exposed to Hg. El-Fawal 1999</td>
<td>Anti-MBP Singh 1993 and 1998</td>
</tr>
<tr>
<td>ANAs found in exposed workers Bigazzi 1994 and Moszcynski 1999</td>
<td>Anti-temporal lobe IgG and IgM Connolly 1999</td>
</tr>
<tr>
<td>MeHg exposed mice Hultman 1999</td>
<td>Anti-serotonin receptor Singh 1997</td>
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<tr>
<td>Anti-serotonin receptor Singh 1997</td>
<td>Anti-nerve growth factor Kozlovskai 2000</td>
</tr>
<tr>
<td><strong>Abs perpetuate without continued exposure</strong> Powell 1999</td>
<td>Other antibodies:</td>
</tr>
<tr>
<td></td>
<td>ANAs Comi 1999</td>
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<td></td>
<td>Anti-small bowel Torrente in press</td>
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## Autoimmunity: genetics

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<tr>
<td>Development of autoimmunity with Hg exposure depends on complex genetics:</td>
<td>Complex genetics of autism</td>
</tr>
<tr>
<td>In all rodent models, immune effects are very dependent upon the strain used. Hu 1997 and Johansson 1998</td>
<td>Family histories of autoimmune disease, especially in mother (rheumatoid arthritis, lupus, IDDM) Comi 1999</td>
</tr>
<tr>
<td>In humans, only some exposed show immunologic effects or develop autoimmune disease. Moszcynski 1999</td>
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# Immunomodulatory treatment

<table>
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<tr>
<td><strong>Responds to IVIG:</strong></td>
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</tr>
<tr>
<td>Case report of man with proteinuria, recurrent infections, and severe gastrointestinal symptoms after exposure to Hg had good response to IVIG  McCann 1995</td>
<td>Improvement in symptoms of autism  Gupta 1996 and Knutsen 1998</td>
</tr>
</tbody>
</table>
Immunotoxicant susceptibility

- Dose of mercury that induces immune effects is less than the dose causing toxicity  (Ilback 1991)
- Developing perinatal immune system more susceptible to MeHg in mice  (Thuvander 1996) and in rats  (Ilback 1991)
- Individual variation is important: “The immune effects of Hg exposure are not necessarily dependent on the dose-response relationships usually applied to toxicological studies, but individual susceptibility plays a more important role.”  (Ellingsen 1994)
- Immune effects of MeHg are synergistic with the suppression caused by other metals such as lead and arsenic.  (Blakley 1980)
Exposure to thimerosal
neonatal
gestational?

Genetically susceptible host
poor elimination toxicokinetics
autoimmune predisposition

Effects amplified by
- sensitivity of developing brain
- decreased ability of neonate to eliminate via bile
- milk diet? - recent antibiotics?

Immune effects
Th2 > Th1
immunodysregulation

CNS damage
direct injury
release of antigens

Autoantibodies to multiple brain components
which can perpetuate without continued exposure
Diagnostic Criteria Met

- The diagnostic traits of ASD are found in cases of HgP.
- The diagnostic criteria of HgP are met in ASD.

### Diagnostic Criteria

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References


El-Fawal HAN et al., Exposure to methylmercury results in serum autoantibodies to neurotypic and gliotypic proteins. *Neurotoxicol* 1996;17(2):531-540.
References


Hu H et al., Pretreatment of lymphocytes with mercury in vitro in T cells from genetically determined low-responders and a induces a response shift of the interleukin profile. *Immunology* 1997;90:198-204.
References

Hu H et al, Mechanism of mercury-induced autoimmunity: both T helper 1- and T helper 2-type responses are involved. *Immunology* 1999;96:348-357.


References


References
Thuvander A et al., Immunomodulating effects after perinatal exposure to methylmercury in mice. *Toxicology* 1996;114:163-175.