

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

Jane Maroney El-Dahr, M.D.

Chief, Section of Pediatric Allergy/Immunology/Rheumatology
Tulane University Health Sciences Center

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Thimerosal-Containing Vaccines and Neurodevelopmental Outcomes

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The Autism – Mercury Hypothesis

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Autism: A Novel Form of Mercury Poisoning. *Medical Hypothesis* 2001;56(4):462-471.

- **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 2nd or 3rd 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.**

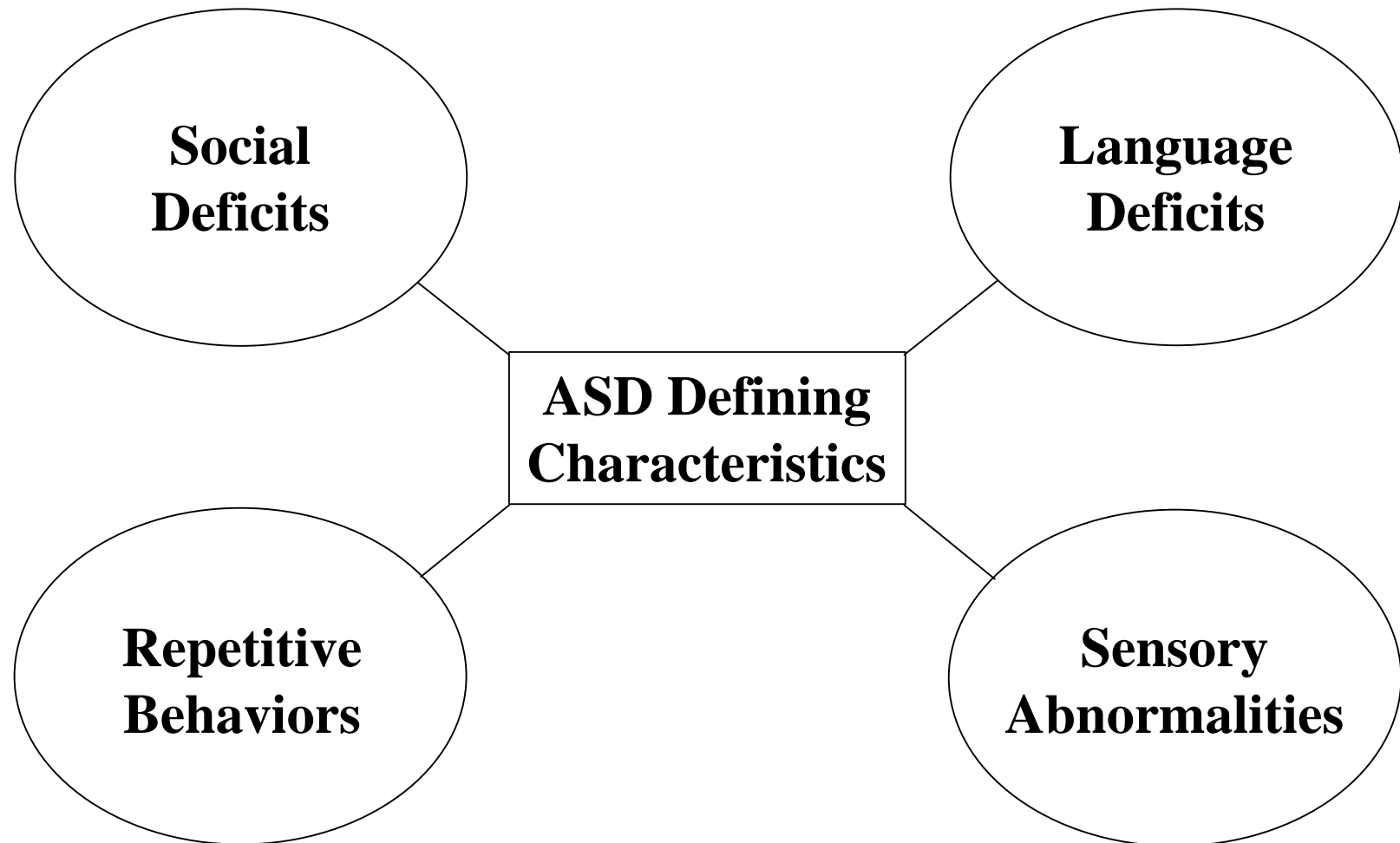
Diagnostic Criteria

Autism
Social deficits
Communication impairment
Repetitive behaviors
[Sensory abnormalities]

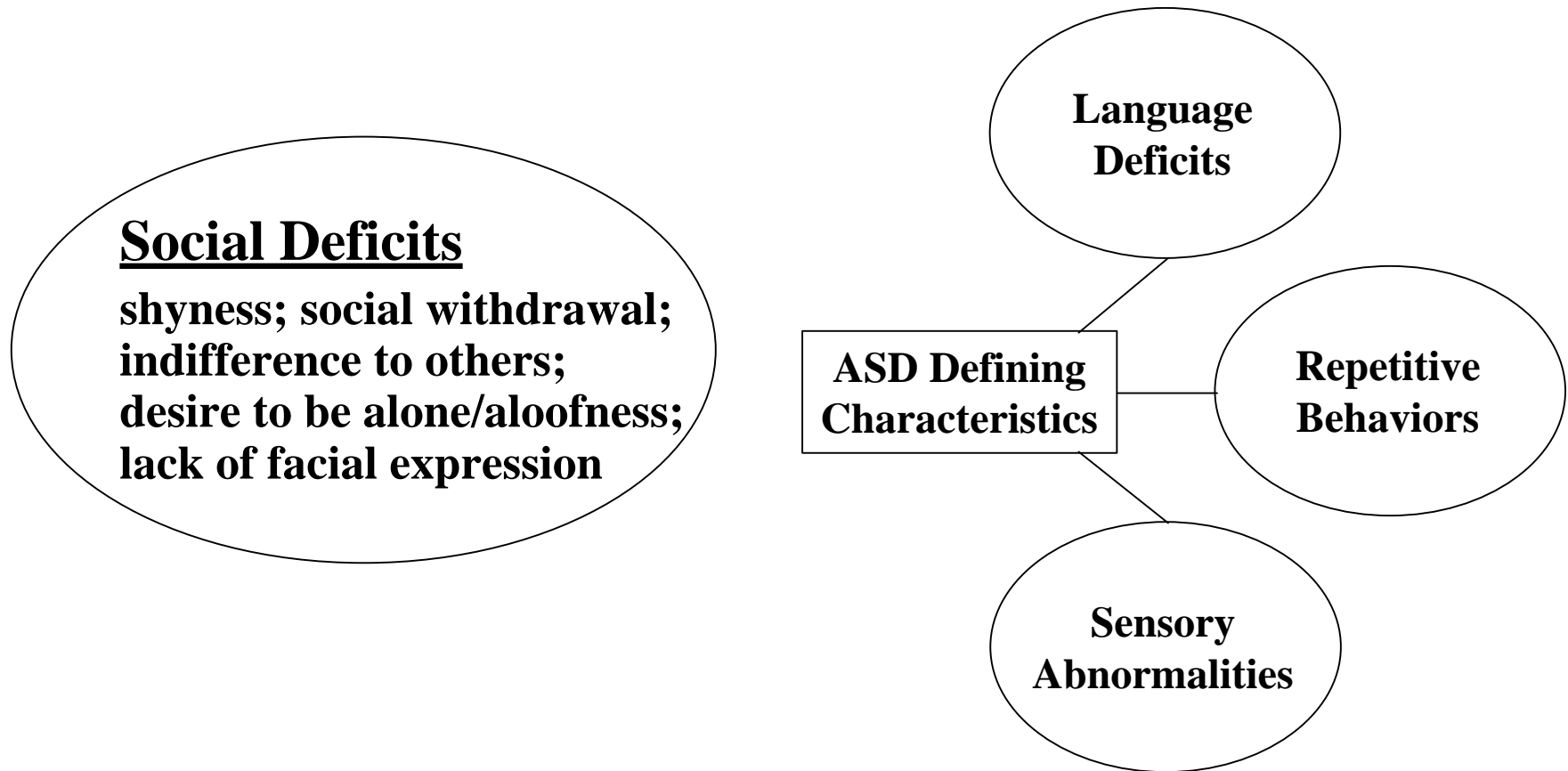
Mercury Poisoning
Symptoms consistent with past cases
Known toxic exposure
Exposure at time of symptom onset
Elevated biomarker Hg concentration

Trait Comparisons

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



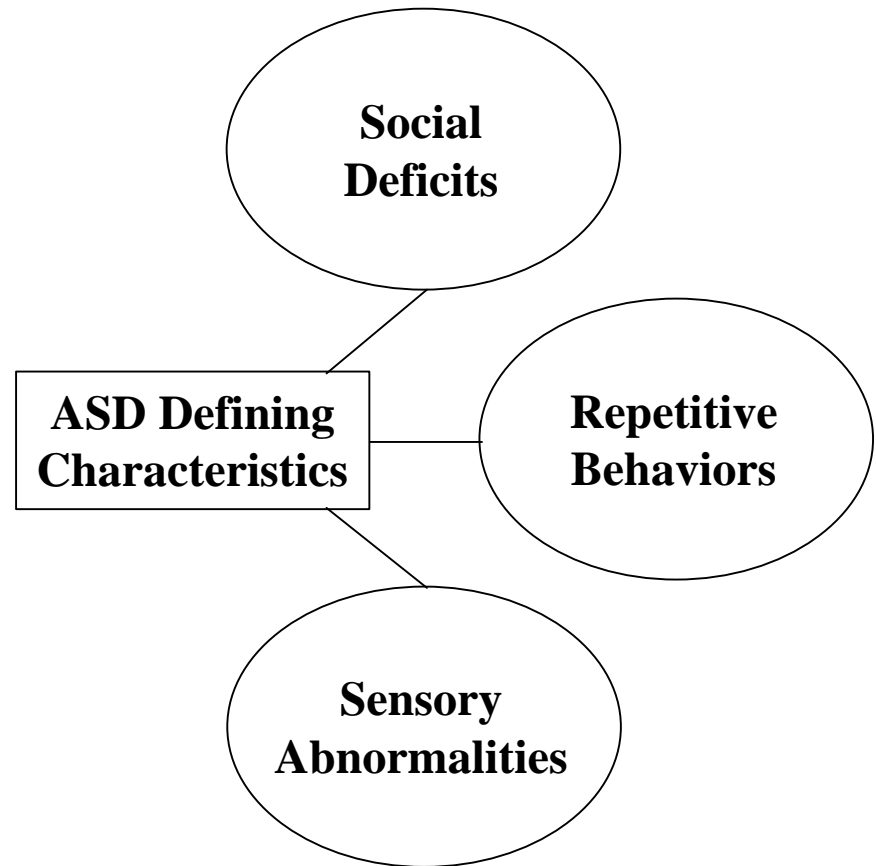
Trait Comparisons – Core Characteristics of ASD also described in HgP Literature



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



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

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graph TD; A[ASD Defining Characteristics] --- B(Social Deficits); A --- C(Language Deficits); A --- D(Repetitive Behaviors);
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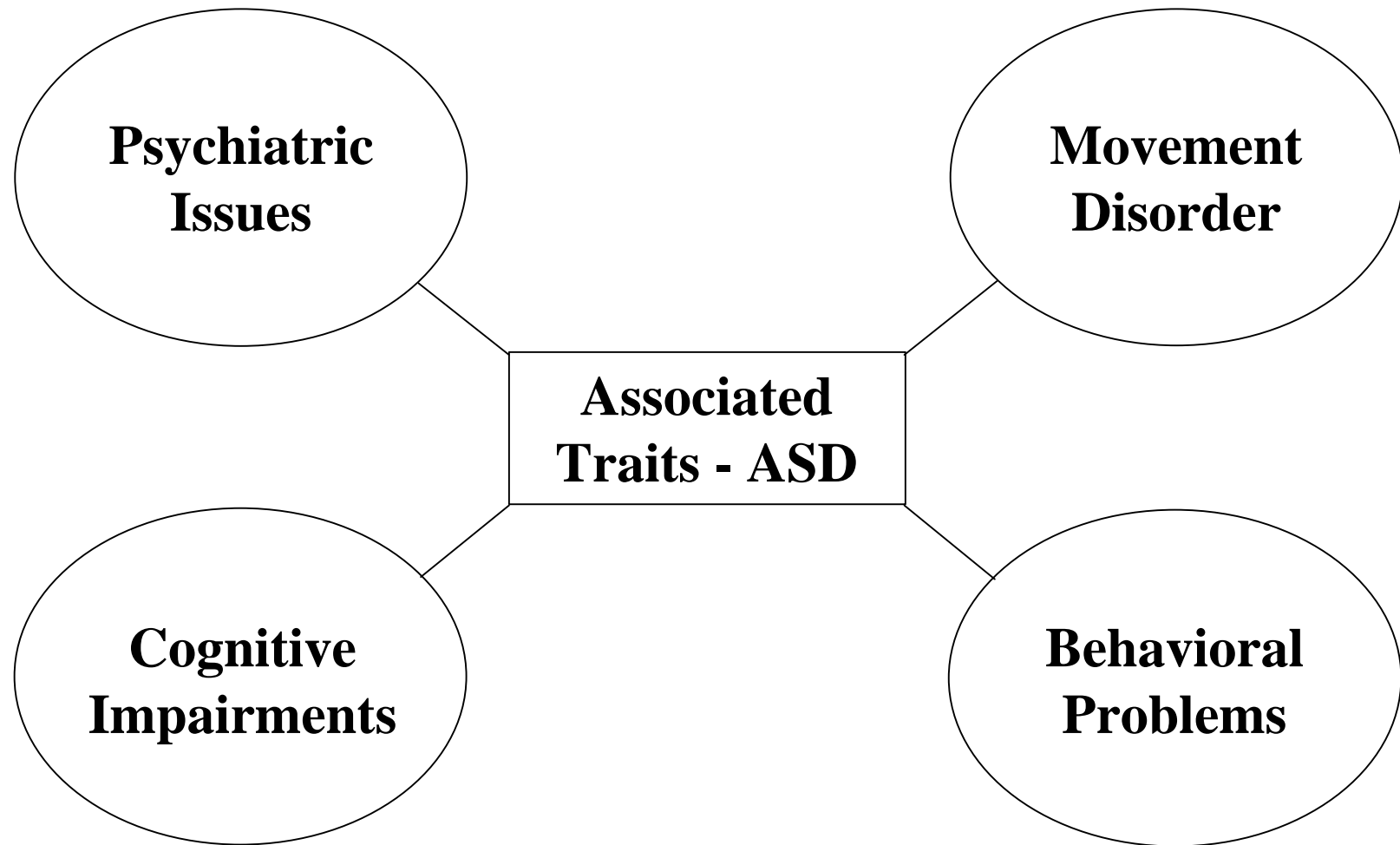
Social Deficits

Language Deficits

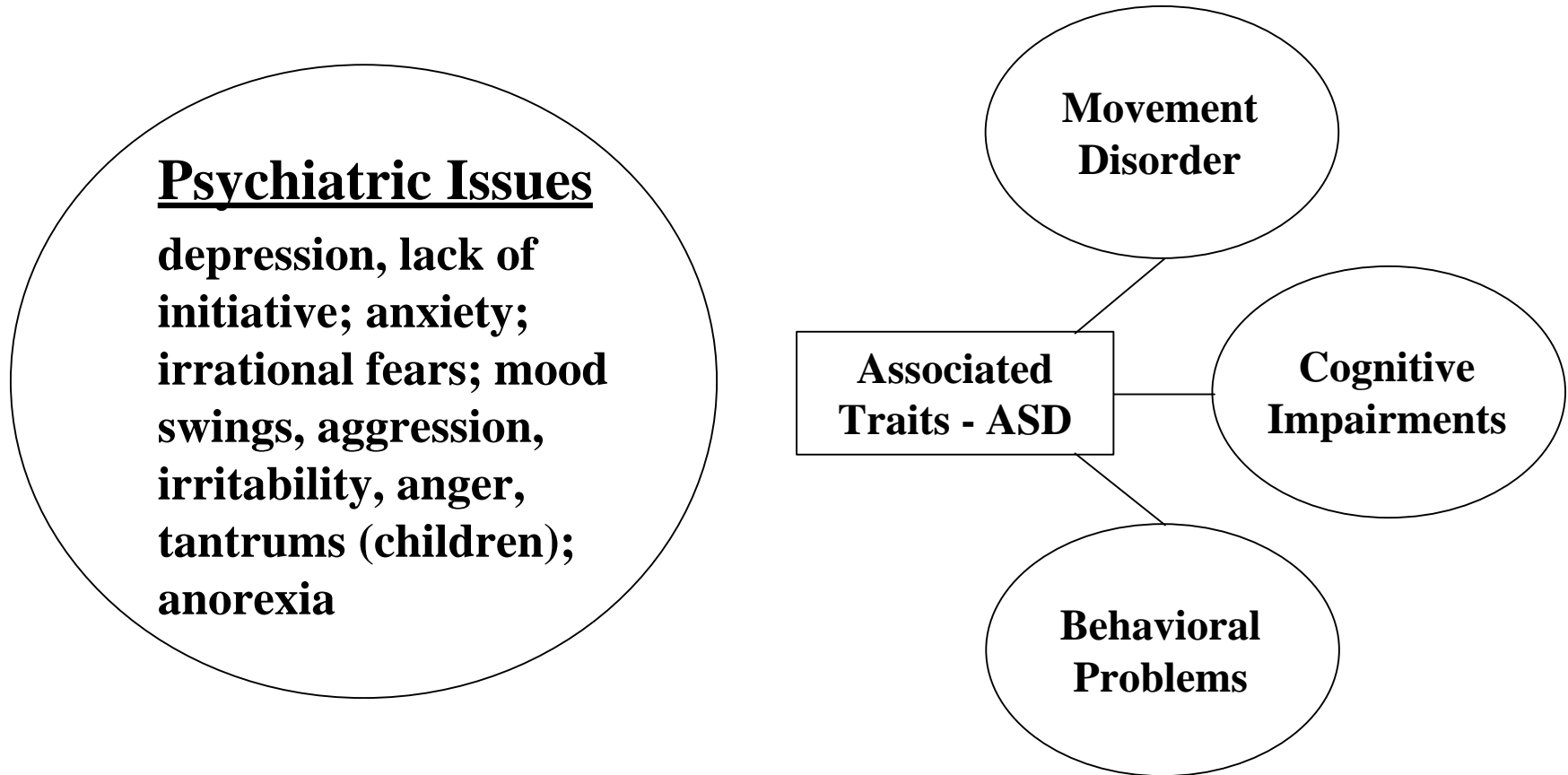
Repetitive Behaviors

Trait Comparisons

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



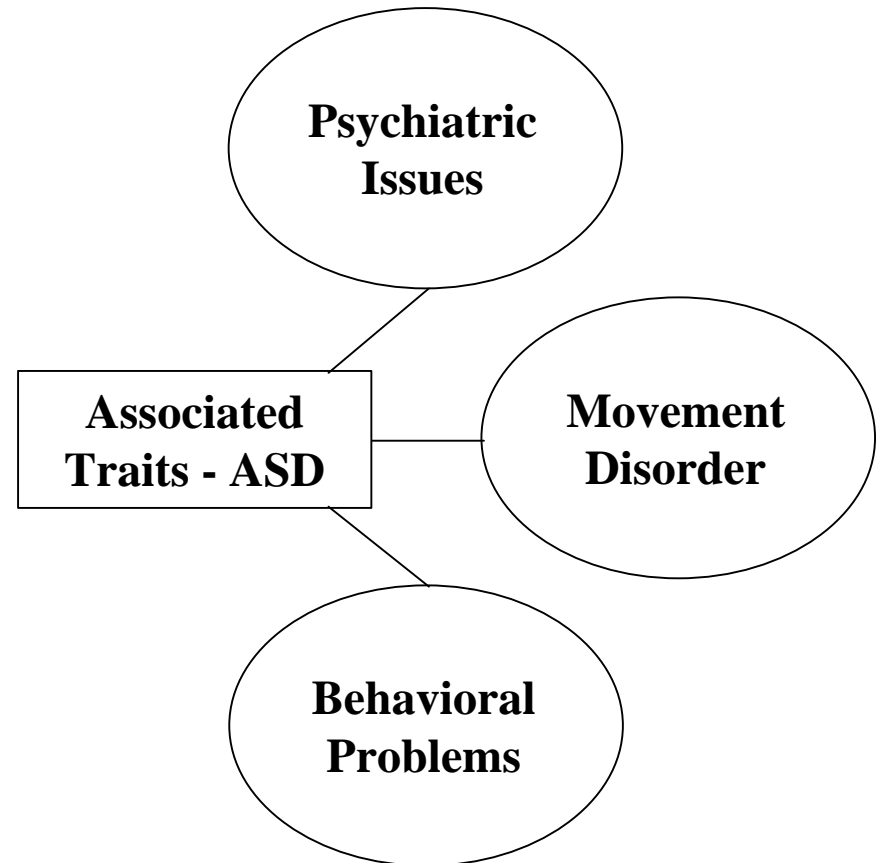
Trait Comparisons – Associated Traits of ASD also described in HgP Literature



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

Cognitive Impairments

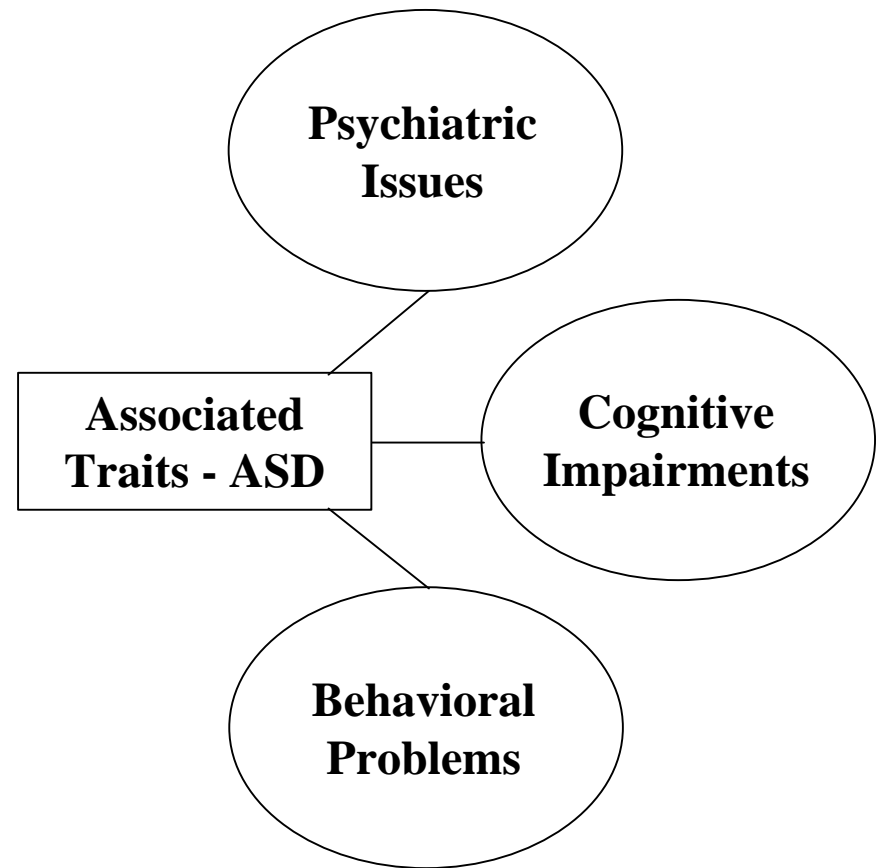
poor performance on language vs. performance IQ; attention deficits; short term, verbal, and auditory memory impairments; mental retardation/deterioration; executive function deficits; difficulty with multi-step commands; deficits in abstract thinking; impaired face recognition



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

Movement Disorder

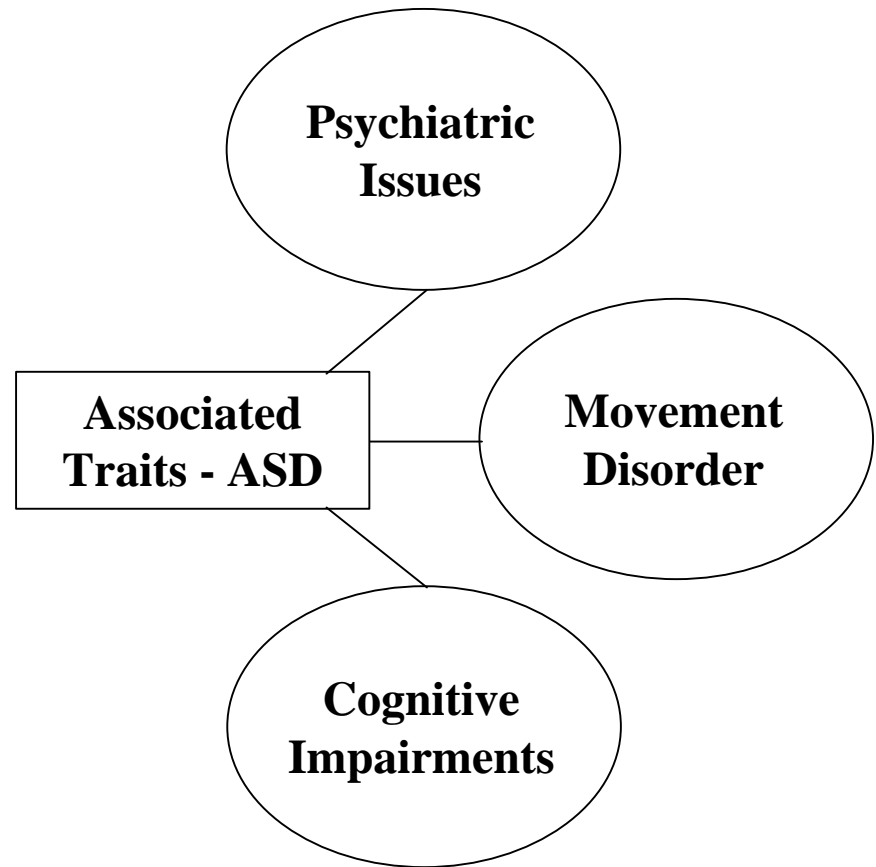
difficulties sitting, crawling, standing, walking, & tendency to fall to one side (infants/toddlers); handwriting difficulties; limb apraxia/poor imitation; clumsiness; abnormal gait or posture



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



Comparisons of Biological Abnormalities in ASD and HgP

CNS - Structure
Neurochemistry
Neurophysiology
Autonomic disturbances
Biochemical
Gastrointestinal
Physical/Muscle Function
Immune System

Biologic Abnormalities – Similarities between Hg and ASD

	Hg	ASD
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 Function	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

Acrodynia/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:

Hg

ASD

<p>Immune dysregulation Hu 1999 and Bagenstose 1999</p> <p>Th2 predominance with high IgE : mouse pups and MeHg Thurvander 1996 High IgE in exposed workers Dantas 1997</p>	<p>Immune dysregulation common predisposes to viral/fungal infections</p> <p>Th2 predominance with decrease in Th1 cytokines Gupta 1998 Increased IgE in 68% Gupta 1999</p>
<p>Increased reactivity to foods: IgE and IgG antibodies made after a single oral dose of Hg Watzl 1999</p>	<p>Increased reactivity to foods: IgE, IgA, IgG Abs in high amounts Lucarelli 1995 T cell reactivity to food in 75% Jyonouchi 2001</p>
<p>Increased permeability of intestinal epithelium Watzl 1999</p>	<p>Increased permeability of intestines 43% vs 0% controls D'Eufemia 1996 76% Horvath 1999</p>

Immune Findings:

Hg

ASD

<p>Alters CD95-mediated apoptosis: small amounts of Hg cause human T cells to undergo apoptosis Shenker 1998 MeHg as well Shenker 2000</p>	<p>Apoptosis increased; nerve cells more susceptible when exposed to low concentrations of thimerosal than controls Gupta DAN 5/11/01</p>
<p>Decreases Natural Killer (NK) cells: Prenatal and/or postnatal exposure to MeHg in rat pups resulted in 57% decrease in NK cell activity. Wild 1997 MeHg exposure in adult mice resulted in 44% decrease in NK cell activity. Ilback 1991</p>	<p>Decreased NK cells: 40% of children studied had abnormally low NK cell activity. Warren 1987 Well over 50% in my practice have decreased NK cell numbers.</p>
<p>Increases chronicity of viral infections: MeHg in mice enhances viral virulence Koller 1975 and viral persistence Ilback 1996</p>	<p>Frequent viral infections common</p>

Autoimmunity: anti-brain antibodies

Hg

Multiple types of **serum anti-brain antibodies** found in rats exposed to MeHg and in humans with Hg⁰.

Rats develop anti-MBP, Anti-NAFP and anti-GFAP El-Fawal 1996

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

ANAs found in exposed workers
Bigazzi 1994 and Moszcynski 1999

MeHg exposed mice Hultman 1999

Abs perpetuate without continued exposure Powell 1999

ASD

Many kinds of **serum anti-brain antibodies** found:

Anti-MBP Singh 1993 and 1998

Anti-NAFP and anti-GFAP
Singh 1997 and Plioplys 1989

Anti-temporal lobe IgG and IgM
Connolly 1999

Anti-serotonin receptor Singh 1997

Anti-nerve growth factor Kozlovskaja 2000

Other antibodies:

ANAs Comi 1999

Anti-small bowel Torrente in press

Autoimmunity: genetics

Hg

Development of autoimmunity with Hg exposure depends on **complex genetics**:

In all rodent models, immune effects are very dependent upon the strain used. Hu 1997 and Johansson 1998

Toxicokinetics of Hg elimination influence expression of autoimmunity. Hultman 1998

In humans, only some exposed show immunologic effects or develop autoimmune disease. Moszcynski 1999

ASD

Complex genetics of autism

Family histories of autoimmune disease, especially in mother (rheumatoid arthritis, lupus, IDDM) Comi 1999

MHC types predisposing to autoimmunity over represented but genetics complicated. Warren 1996 and 1998

Immunomodulatory treatment

Hg

ASD

Responds to IVIG:

Case report of man with proteinuria, recurrent infections, and severe gastrointestinal symptoms after exposure to Hg had good response to IVIG McCann 1995

Responds to IVIG:

Improvement in symptoms of autism Gupta 1996 and Knutsen 1998

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?

plus

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

Autism	in HgP?
Social deficits	√
Communication impairment	√
Repetitive behaviors	√
[Sensory abnormalities]	√

Mercury Poisoning	in ASD?
Symptoms of past cases	√
Known toxic exposure	√
Exposure at time of symptom onset	√
Elevated biomarker Hg concentration	√

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