OXIDATIVE STRESS IN AUTISM SPECTRUM DISORDERS

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Walsh Research Institute

- **Nonprofit public charity**
- **Experimental research**
- **Expertise in biochemical therapy**
- **International physician training**

Clinical Experience

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- 10,000 Behavior & ADHD
- 6,500 Autism-Spectrum Disorder
- 6,500 Mental Illness

Autism Spectrum Database

- About 90 to 150 assays of chemical factors in blood, urine, or hair for each of 6,500 patients,
- More than 800,000 chemical test results,
- Comparison with known “normal” levels.

Autism Database Analysis

- Major biochemical abnormalities observed in the autism population.
- Autism biochemical imbalances are more severe than those for violent behavior, depression, and schizophrenia.
- Female autistics have more disordered chemistry than male autistics.

High Incidence Biochemical Abnormalities in Autism

- **Depressed Glutathione & Cysteine**
- **Elevated toxic metals**
- **Depressed SAMe/SAH Ratio**
- **High Copper & low Ceruloplasmin**
- **Depleted Zinc & Metallothionein**
- **Elevated Pyrroles**
- **Low B-6, C, and Selenium**
- **Elevated Urine Isoprostanes**

Note: Each of these imbalances is associated with elevated OXIDATIVE STRESS.

Oxidative Stress and Autism

1. Excessive oxidative stress is evident throughout the autism spectrum,
2. An oxidative stress model can explain most symptoms of autism,
3. Most autism therapies have antioxidant properties,
4. Oxidative stress has become a leading focus of autism research.

What Is Oxidative Stress?

- Excess of chemical free-radicals that can destroy cells, proteins, and essential fats.
- Free-radicals are atoms or molecules with unpaired electrons that are unstable and highly reactive,
- Reactive oxygen specie (ROS) include superoxide, hydroxyl radicals, and hydrogen peroxide,
- Mercury, lead, and other toxic metals induce free-radical stress.

Consequences of Oxidative Stress Mirror Classic Symptoms of Autism

- Hypersensitivity to Hg and other toxic metals
- Hypersensitivity to certain proteins (casein, gluten, etc)
- Poor immune function
- Disruption of the methylation cycle
- Inflammation of the brain & G.I. tract
- Depletion of glutathione & metallothionein
- Excessive amounts of “unbound” copper

Most Popular Autism Therapies Enhance Antioxidant Protection

- Chelation with DMSA, DMPS, EDTA, etc.
- Methyl B-12
- Metallothionein Promotion
- Transdermal or Injected Glutathione
- Zn, Se, CoQ-10, Taurine, Vitamins A,C,D,E
- Alpha Lipoic Acid
- Risperdal

Distinctive Features of Autism

- Strong genetic predisposition
- Onset after environmental insult
- High oxidative stress
- Incomplete brain maturation

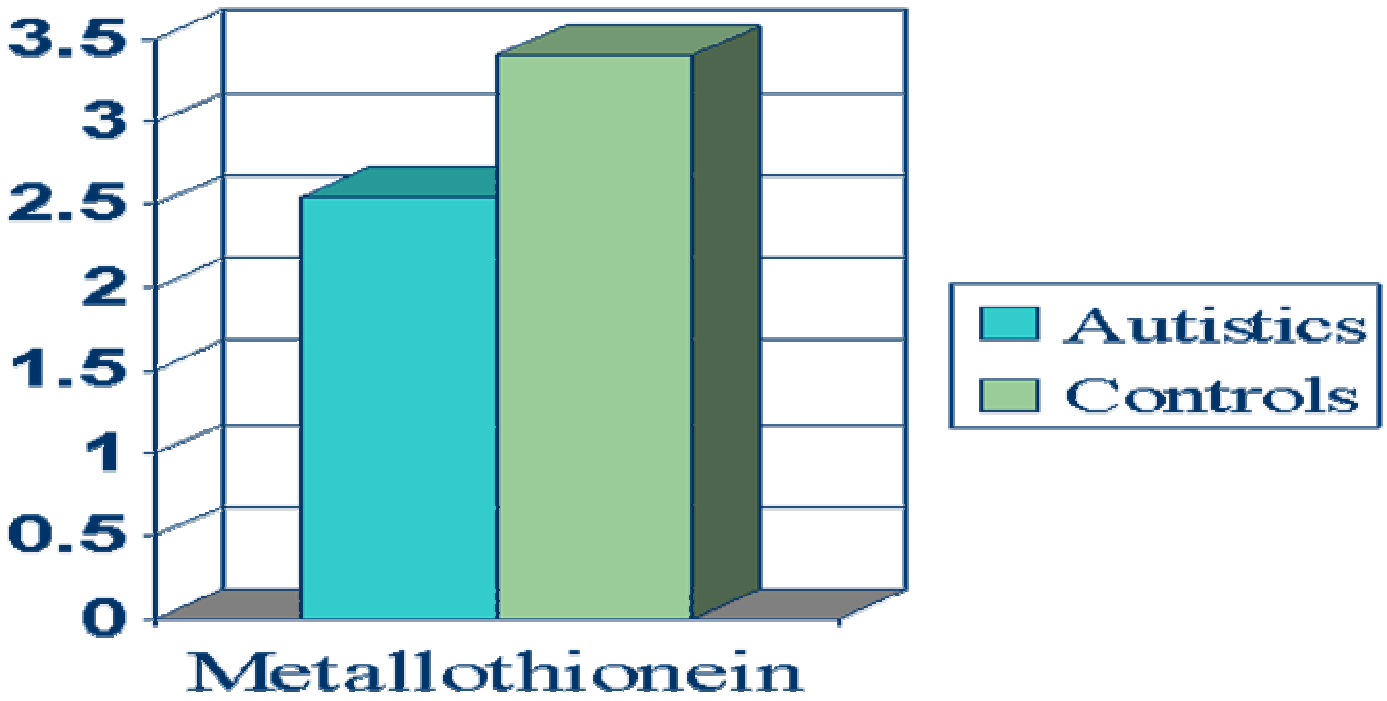
Autism Brains Are Different

- Incomplete maturation – Excessive number of short, undeveloped brain cells in cerebellum, amygdala, pineal gland and hippocampus,
- Poverty of brain dendrites and synapses,
- Narrowed minicolumns in brain cortex,
- Brain inflammation and increased head size,
- High oxidative stress,
- Abnormal levels of calcium and iron,
- Damaged DHA and other brain lipids.

Oxidative Stress Can Impair Brain Development

- MT is required for pruning, growth and growth-inhibition of brain cells in early development,
- Ample GSH is required for proper MT function,
- MT and GSH are depleted in autism,
- High oxidative stress depletes MT and GSH.

Low Metallothionein Levels in Autism
# $p < 0.0092$



Why is Metallothionein Important?

- Required for development of brain cells and synaptic connections,
- Prevents Hg, and other metal toxics from passing intestinal and blood/brain barriers,
- Required for homeostasis of Cu and Zn,
- Supports immune function.

Note: MT functioning can be disabled by excess oxidative stress.

Consequences of Oxidative Stress Overload in the G.I. Tract

- Destroys digestive enzymes needed to break down casein & gluten,
- Increases candida/yeast levels,
- Diminishes Zn levels and production of stomach acid,
- Produces inflammation,
- Results in a “leaky” intestinal barrier, allowing toxics to enter the bloodstream.

Oxidative Stress and Methylation
The Chicken or the Egg?

- Excess oxidative stress can deplete GSH, impair the one-carbon cycle, and produce undermethylation.
- Undermethylation can reduce production of GSH, cysteine, and MT, and cause excess oxidative stress.
- A genetic weakness in either factor can produce the other.
- Both factors are distinctive features of autism.

Autism Rates
A Continuing Medical Mystery

- Strong genetic predisposition: Greater than 60% concordance in identical twins; Less than10% concordance in fraternal twins,
- Dramatic increase in autism cases over the past 50 years.
- Autism rates continue to escalate – October, 2009 data indicates one case per 100 births.

How can there be an epidemic of a genetic condition?

The Role of Environment

Concordance of only 60-80% in identical twins indicates that environment plays a major role.

Conclusion

Since DNA mutations can take centuries to develop, the autism epidemic has been attributed to changes in environment.

The Recipe for Autism

1. Genetic Predisposition

2. Environmental Insult

Environmental Insults: A Multitude of Possibilities

1. Attention has been focused on direct insults to the child from conception to age three.

2. More than 25 environmental insults have been proposed, including mercury exposures, vaccines, changes in diet, viruses, increased Cu in the water supply, etc, etc.

Another Possibility - Epigenetics

- Chemical insults during the first month of gestation can produce abnormalities in gene expression that may persist throughout life.
- In some cases, these abnormalities can be transferred to future generations.
- This could result in a geometric increase in the number of autism-prone families.

Epigenetic Processes During Early Fetal Development

- Every cell has the potential for expressing any of the >20,000 genes in DNA,
- In utero chemical environment determines which genes will be expressed or inhibited throughout life (bookmarking),
- Gene expression tendencies can be transmitted to future generations by a process called transgenerational epigenetic inheritance (TEI),
- Methylation is a primary factor in TEI, and is abnormal in autistic children.

A Clue From the Past -- Thalidomide Babies

- Deformed thalidomide babies of the 1960's had a high incidence of autism,
- Published research showed that cases of autism occurred only if the offending sleeping pill was taken between days 20-24 of gestation,
- This is the period when most epigenetic decisions regarding gene expression or inhibition are established,
- This may be the time of greatest sensitivity to environmental insults.

Autism Research Update

- Poverty of brain dendrites & synapses
- Male/Female differences in brain chemistry
- Dominant importance of oxidative stress
- Evidence of neurodegeneration in autism
- Evidence that brain levels of mercury are in the normal range within a few years following significant exposure.

The Final Battlefield – The Brain

- Autism involves a brain that has not completed the maturation process,
- Brain cells and organelles may have been damaged,
- In either case, development of immature brain cells, and production of new dendrites and synapses must be a high priority in autism therapy.

Behavioral Therapies and Brain Plasticity

- ABA stimulates organization of synaptic connections & cortex minicolumns.
- ABA promotes brain maturation, but is greatly slowed by oxidative overload and inflammation.
- ABA is especially promising when coupled with antioxidant therapy.

Hebb's Rule:

Brain cells that fire together, wire together.

Unique Advantages of Metallothionein-Promotion Therapy

- Directly aimed at development of brain cells,
- Potential for permanently correcting the intestinal and blood/brain barriers,
- Restores a key antioxidant system.

Limitation: **Does not directly enhance development of dendrites and synapses.**

New Autism Therapies Needed

There is a critical need for advanced therapies that can accomplish the following:

1. Development of new brain cell dendrites and receptors,
2. Promotion of new brain synapses,
3. Strengthening of cortex minicolumns.

Chelation and Oxidative Stress

- DMSA and DMPS are powerful antioxidants.
- Chelation can provide antioxidant benefits even if toxic metals are **not** present.
- For many patients, the primary benefits of chelation result from antioxidant properties, and not from removal of Hg or other metals.
- Antioxidant benefits from chelation appear to "fade away" after about 2-4 weeks.

Primary Benefits of Chelation

- Rapid removal of toxic metals from peripheral soft tissues & blood, thus preventing their access to the brain,
- Powerful antioxidant

Limitations of Chelation

- Does not fix intestinal or blood/brain barriers, rendering the patient vulnerable to future toxic exposures,
- Antioxidant benefits are temporary, lasting only 2-4 weeks,
- May not remove toxic metals from the brain,
- Complicates Zn management.

Autism and Neurodegeneration

- Increased evidence of neurodegeneration in autism…. attributed to severe oxidative stress,
- Gradual loss of brain cells and IQ may occur in the absence of antioxidant therapy,
- Young autistics appear very bright despite behavioral, speech, and socialization deficits,
- Most adult autistics exhibit mental retardation (exception: Aspergers patients).

Note: Antioxidant therapy may be needed throughout life.

Barriers to Progress

- Oxidative stress retards development of new brain cells and synapses,
- Brain inflammation obscures evaluation of autism therapies.

Treatment Evaluation Problem

Many popular autism therapies merely reduce inflammation, and are overvalued.

1. rapid, striking improvement in symptoms
2. brain maturation remains to be accomplished
3. brain maturation is a slow, gradual process.

Walsh's Law

An autism therapy that produces immediate great improvement has reduced brain inflammation, but hasn't "fixed" the brain.

Important Questions

- Why do most autism regressions occur during months 16-22? Environmental insults are present throughout development.
- Why do many autism regressions result in radical changes in speech, socialization, food sensitivities, etc., in just a few days?
- Why do autism symptoms persist after onset?

Conclusion: A dramatic EVENT has occurred!!

Oxidative Stress Theory of Autism

(Bill Walsh, October, 2009)

- Genetic/Epigenetic predisposition involves weakened defense against oxidative stress,
- Cumulative oxidative insults gradually deplete GSH, MT, SOD and other protective factors,
- A threshold is reached in which antioxidant protection collapses, causing (a) sudden brain & G.I. tract inflammation, (b) leaky intestinal & brain barriers, (c) interruption of normal brain development.

A Strategy for Enhanced Cognition, Speech, and Socialization

- Elimination of excess oxidative stress and inflammation,
- Normalization of blood/brain & intestinal barriers,
- Therapies that enhance brain maturation.

The Bottom Line

OXIDATIVE STRESS MAY BE
THE PRIMARY CAUSE OF AUTISM

1. The genetic predisposition in autism may be weakness in coping with oxidative stress,
2. The environmental component may involve a variety of oxidative insults.

THANK YOU!

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