

# Neurological Abnormalities in ASD

## ASD and Epilepsy

Individuals with autism spectrum disorder (ASD) have a 3 to 22-fold increase in the risk of developing epilepsy as compared to typically developing individuals and **up to 25% of individuals with ASD will experience clinical seizures at some point in their life.** It is interesting (and I have seen this in practice a number of times) that a significant number of individuals with ASD manifest epileptic brain wave abnormalities on a brain electroencephalograph (EEG), **despite a lack of clinical seizures.**

The prevalence of **treatment-resistant epilepsy** in children with ASD is believed to be higher than in the general childhood population. Despite the fact that ASD individuals with seizures appear to represent a large ASD subgroup, traditional seizure treatments for individuals with ASD have not been well studied and potential novel therapies tend not to be discussed. The first-line treatment for any child with seizures is anti-epileptic drug therapy. The poor efficacy and/or adverse effects of antiepileptic drugs in individuals with ASD may prompt the use of traditional or novel non-epileptic drug treatments. Additionally, since seizures in ASD are associated with specific genetic and metabolic syndromes (e.g. mitochondrial dysfunction), therapies that target these syndromes may augment traditional treatments for epilepsy.

### Genetic and Metabolic Syndromes associated with Epilepsy and ASD

- ◆ Mitochondrial disease and dysfunction
- ◆ Abnormalities in folate metabolism
- ◆ Urea cycle disorders
- ◆ Succinic semialdehyde dehydrogenase deficiency
- ◆ Creatine deficiency syndromes
- ◆ Biotinidase deficiency
- ◆ Smith–Lemli–Opitz syndrome
- ◆ Branched-chain ketoacid dehydrogenase kinase deficiency
- ◆ Pyridoxine-dependent and pyridoxine responsive seizures
- ◆ Abnormalities in cobalamin metabolism
- ◆ Organic acidurias

Appropriate testing can identify some of the genetic or metabolic issues in the above list. Blood tests, **organic acid testing (OAT)** and tests for gene polymorphisms (**MTHFR**) can identify underlying problems and guide appropriate treatment.

### Novel Treatments for ASD with Epilepsy

- ◆ Ketogenic diet
- ◆ Gluten/casein free diet
- ◆ Hyperbaric oxygen therapy
- ◆ Vitamin B6
- ◆ Carnitine
- ◆ CoQ10
- ◆ Vitamin B12
- ◆ Dimethylglycine
- ◆ Taurine
- ◆ GABA
- ◆ Magnesium
- ◆ 5-hydroxytryptophan
- ◆ L-carnosine
- ◆ Glutathione
- ◆ Specific Carbohydrate Diet

Supporting the nervous system to ensure adequate nutrients are present to support optimal nerve myelination, receptor function, nerve conduction, etc, is essential.

Clinical characteristics of children with autism spectrum disorder and co-occurring epilepsy. Viscidi EW, Triche EW, Pescosolido MF, McLean RL, Joseph RM, Spence SJ, et al. *PLoS One* (2013) 8:e67797. doi:10.1371/journal.pone.0067797

A review of traditional and novel treatments for seizures in autism spectrum disorder: findings from a systematic review and expert panel. Richard E. Frye, Daniel Rossignol, et al. *Frontiers in Public Health*. September 2013 | Volume 1 | Article 31. doi: 10.3389/fpubh.2013.00031

Traditional and non-traditional treatments for autism spectrum disorder with seizures: an online survey. Richard E Frye, Swapna Sreenivasula and James B Adams. *BMC Pediatrics* 2011 11:37.



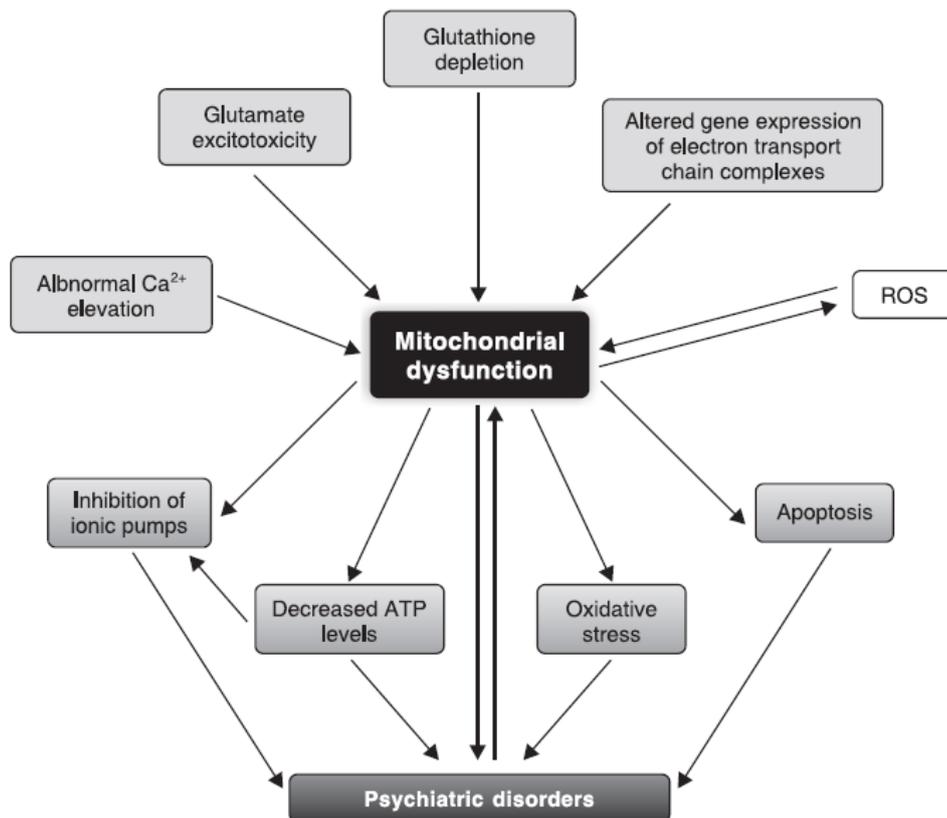
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Changing the  
way we think  
about treating  
autism.

## Brain Mitochondrial Dysfunction in ASD

Evidence that mitochondrial dysfunction is a biological subtype of ASD has grown over the years. Studies are now showing that mitochondrial dysfunction is present in brain tissue. The brain relies heavily on energy and metabolism and mitochondrial dysfunction can lead to a wide range of neurodevelopmental disorders (depression, bipolar disorder, anxiety disorders, obsessive compulsive disorder and ASD). Substantial percentages of autistic patients display peripheral markers of mitochondrial energy metabolism dysfunction, such as elevated lactate, pyruvate, and alanine levels in blood, urine, and/or cerebrospinal fluid, serum carnitine deficiency, and/or enhanced oxidative stress.



### Symptoms of Mitochondrial Disease / Dysfunction

There are many clinical presentations

- Can affect the eyes, ears, cardiovascular and gastrointestinal systems
- Neurologic
- Movement disorders: Posturing, writhing, jerking
- Hypotonia
  - ◇ Weak suck and swallow
  - ◇ Poor head control; floppy
  - ◇ Drooling
  - ◇ Decreased activity tolerance
  - ◇ Curved back while sitting
  - ◇ Difficulty knowing self in space
  - ◇ Gross and fine motor defects

An **Organic Acid test** can identify abnormalities in mitochondrial function, glutathione production, and oxidative stress.

Mitochondria and the central nervous system: searching for a pathophysiological basis of psychiatric disorders. Emilio L. Streck, Cinara L. Gonçalves, Camila B. Furlanetto, Giselli Scaini, Felipe Dal-Pizzol, João Quevedo. *Revista Brasileira de Psiquiatria*. 2014;36:156–167.

Mitochondrial dysfunction as a neurobiological subtype of autism spectrum disorder: evidence from brain imaging. Goh S, Dong Z, Zhang Y, DiMauro S, Peterson BS. *JAMA Psychiatry*. 2014 Jun 1;71(6):665-71.

## Brain Inflammation and Immune Dysregulation in ASD

It has been known for decades that the immune system has a tremendous impact on behaviour. A well-regulated immune system is needed for proper brain function. It is now becoming apparent that some behavioural deficits in neurodevelopmental disorders, such as in ASD, are the consequence of a malfunctioning immune system.

Evidence of immune involvement in the brain includes the presence of activated immune cells (microglial cells) and inflammatory immune mediators in the brain. Particularly high levels of immune cells have been detected in the areas of the brain involved in speech (the Broca area) and behaviour (the diencephalon). Microglia are immune system cells in the brain that act as the first and main form of active immune defence in the central nervous system (CNS) defending the brain and spinal cord, constantly attacking and engulfing infectious agents and engulfing damaged nerve cells. When microglia are chronically active, they release damaging chemicals.

The source of the chronic immune activation within the brain could include several factors, such as vaccine adjuvants, mercury and aluminium accumulation within astrocytes and microglia, viral fragments or vaccine derived living viruses (either measles virus or contaminant viruses). Autistic children often suffer from repeated systemic infections, usually of the middle ear, which would also act to prime the microglia. A number of studies have shown a cross reaction between food antigens and neuron-specific antigens. For example, some studies have found food antigens in 50 autistic children that cross-reacted specifically with Purkinje neurons in the brain. Another initiator of microglial activation could be *Candida* infection or other colon bacterial infections, which are also reported to be common in children with ASD.

A number of children with ASD have elevated levels of blood and CSF **glutamate** and have specific immune dysfunction, characterized by chronically elevated levels of brain inflammatory cytokines and chemokines, both of which are known to significantly interfere with neurodevelopment.

**Inflammatory cytokines magnify the neurotoxic effects of glutamate significantly.** The immature brain is approximately 4-times more sensitive to glutamate excitotoxicity as the adult brain. An explanation for hypersensitivity of the immature brain lies in the observation that during brain development the NMDA (*N*-methyl-D-aspartate) receptor is more sensitive to glutamate and less responsive to magnesium protection. **Behavioural studies have also shown that exposure to excess glutamate during critical periods of brain development can produce prolonged alterations in behaviour.** Animal studies have shown that behavioural effects are more common in male animals, with few effects being found in the female animals. Affected males showed little social interest in their littermates, demonstrated defects in novelty and perceptual mechanisms and an inability to focus attention, again all characteristics of children with ASD disorders.

Experimentally, **vitamin E, thiamine, riboflavin, pyridoxine, methylcobalamin, folate, and nicotinamide** have been shown to significantly reduce glutamate toxicity *in vitro*. **Vitamin B6** can dramatically lower blood and tissue glutamate levels and raises seizure thresholds.

Some children with autism have **autoantibodies** that target brain proteins. Similarly, some mothers of children with autism produce antibodies specific to autism that target foetal brain proteins. **Children with such autoantibodies towards brain proteins are associated with lower adaptive and cognitive function as well as core behaviours associated with autism.** It is unclear whether these antibodies have direct pathologic significance, or if they are merely a response to previous injury.

Focal brain inflammation and autism. Theoharis C Theoharides, Shahrzad Asadi, and Arti B Patel. Journal of Neuroinflammation 2013, 10:46 doi:10.1186/1742-2094-10-46.

Immune-Glutamatergic Dysfunction as a Central Mechanism of the Autism Spectrum Disorders. R.L. Blaylock and A. Strunecka. Current Medicinal Chemistry, 2009 Vol. 16, No. 1.

Autoantibodies to cerebellum in children with autism associate with behavior. Goines P; Haapanen L. et al. Brain Behav Immun. 2011; 25 (3):514-23

## Oxidative Stress in the ASD Brain

A number of studies have reported evidence of oxidative stress in post-mortem brain samples obtained from individuals with ASD compared to controls. These studies have demonstrated:

- a decrease in glutathione (GSH), the major cellular antioxidant
- oxidative damage to proteins, lipids and deoxyribonucleic acid (DNA)
- alternations in the activity of enzymes important in redox metabolism

Interestingly markers of GSH metabolism do not correlate with age, suggesting that the oxidative stress observed is a chronic condition in ASD. One of the first studies reported a significant increase in lipofuscin containing cells, a marker of oxidative stress, in 3 language areas of the brain in males with autism compared to male controls. Other studies have documented significant oxidation of proteins (including oxidation of DNA) in ASD brain tissue. There are many lines of evidence supporting the notion of increased levels of oxidative stress in 5 key regions of the brain to lipid and proteins in individuals with ASD.

One line of thought is whether it is possible that the reduced transportation of folate into the brain is due to a folate receptor alpha autoantibody (see: Cerebral Folate Deficiency article) or mitochondrial dysfunction that could reduce the function of methylation and glutathione metabolism specifically within the brain leading to some of the findings described above. However, many of these same findings reported in the brain (oxidative damage to lipids, protein and DNA, glutathione abnormalities, reduced function of enzymes essential for regulating oxidative stress) have been found in the blood, immune cells and cell lines derived from individuals with ASD, thereby raising the question of whether these findings are specific for the brain or whether they represent a more general process.

Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. Daniel A. Rossignol and Richard E. Frye. *Frontiers in Physiology*. April 2014, Volume 5, Article 150.

## Additional Considerations as ASD Children Mature

As our children grow, we are focussed on behaviour, language development, social skills, academic skills, etc. However, as high functioning children grow and are able to gain independent living skills, as a parent of a adult ASD son, I know there are other issues that do arise, which parents should be prepared for.

In the ASD population, there is a higher incidence of neuropsychiatric disorders:

- Adults with ASD report significantly **higher stress and poorer ability to cope with stress** in everyday life, as compared to typical adults.
- **Anxiety** is high amongst young ASD adults, which may be due to social anxiety and general anxiety in performing daily tasks.
- **Bipolar disorder** in Asperger syndrome patients is frequent, onset is usually during adolescence and is often characterized by an atypical presentation. This makes correct diagnosis particularly difficult, individuals often have many different diagnoses before receiving a correct diagnosis.
- Individuals with Asperger syndrome may be **at higher risk for attempting suicide** compared to the general population.

Supporting children from an early age to maximise their brain biochemistry minimises the possibility of developing mood or psychiatric disorders as they grow into adults.

High self perceived stress and poor coping in intellectually able adults with autism spectrum disorder. Hirvikoski T, Blomqvist M. *Autism*. 2014 Jul 29.

A Systematic Review of Treatments for Anxiety in Youth with Autism Spectrum Disorders. Vasa RA, Carroll LM, Nozzolillo AA, Mahajan R, Mazurek MO, Bennett AE, Wink LK, Bernal MP. *J Autism Dev Disord*. 2014 Jul 29.

Bipolar disorder in adults with Asperger's Syndrome: A systematic review. Vannucchi G, Masi G, Toni C, Dell'Osso L, Erfurth A, Perugi G. *J Affect Disord*. 2014 Jul 8;168C:151-160.

History of suicide attempts in adults with asperger syndrome. Paquette-Smith M, Weiss J, Lunskey Y. *Crisis*. 2014 Jan 1;35(4):273-7.