The Pathophysiology of Autism
La fisiopatología del autismo

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ABSTRACT
Autism has been classically defined by its behavioral symptoms. Traditional medical research has focused on genetic or intrinsic brain-based causes of autism. While both of these are important, additional research has focused on the underlying disordered biochemistry seen in many individuals with autism. Many of these biomedical factors are amenable to treatment. This article will review the main pathophysiologic factors seen in individuals with autism spectrum disorders.

INTRODUCTION
Autism is a behavioral/developmental disorder characterized clinically by delays and qualitative differences in communication and social interaction as well as repetitive behaviors and restricted interests. Theories of the causes of autism have evolved over time from the concept of “refrigerator mothers,” a discredited theory purporting that children became autistic due to the inability to bond with cold, unfeeling mothers, to that of a more educationally and behaviorally based disorder. Traditional diagnostic investigations have focused primarily on genetic or intrinsic brain causes of autism. Newer paradigms, however, are focusing on the potential role of a myriad of biochemical and systemic factors that may be extrinsic to the brain but having secondary effects on the brain. This way of thinking allows for the possibility of a paradigm shift from viewing autism as a static, unchangeable, lifelong disorder to one that is more dynamic and potentially amenable to treatment. This article reviews the current state of knowledge regarding potential underlying biomedical factors contributing to symptoms of autism, ie, the pathophysiology of autism spectrum disorders (ASDs).

The prevalence of autism has risen dramatically in the past 2 decades. The most recent US Centers for Disease Control and Prevention data from 2008 reports a prevalence of 1 in 88 children in the United States, in 54 in boys, and an increase of 78% during the 6-year period from 2002 to 2008. There are many potential reasons for this increase. Non-biomedical reasons cited include an increase in diagnostic awareness, broadening of the diagnostic criteria, and diagnostic relabeling (ie, labeling children who previously had different labels as autistic). All of these are partial explanations for this increase but alone cannot account for the staggering increase in numbers of children with autism. Underlying contributing biomedical factors resulting from a combination of genetic vulnerability plus environmental triggers, with consideration of “environment” in a broad sense, are additional factors likely contributing to this increase.

Traditional medicine has been directing its genetic focus toward identifying the gene or genes responsible for autism. However, the picture emerging is much more complex than anticipated, with multiple potential genes being contributory to some degree along with the emerging awareness of “epigenetics.” Epigenetics is the effect on gene expression without a change in the base pairs; it is what happens around the gene. These epigenetic effects can have ramifications on an individual’s health from fetal developmental through the lifetime (and potentially transgenerationally) and so are profoundly important. Epigenetic effects can affect early cortical development and therefore may play a role in autism.
FUNCTIONAL MEDICINE APPROACH

An effective organizing approach to these complex and interconnected biomedical factors is that of functional medicine. Functional medicine involves looking below the surface of the symptoms in order to identify causative factors. A helpful construct is to ask the following two questions when evaluating an individual with autism:

1. Are this individual's body and brain getting what they need to function optimally (eg, vitamins, minerals, omega-3 fatty acids, healthy clean foods)?
2. Is something present in this individual's body and brain that is interfering with his or her ability to function optimally (eg, internally or externally derived toxins, free radicals, cytokines, histamine)?

The goal of answering these two questions is to optimize function by giving the brain and body what they need and eliminating that which may be interfering. From these two simple questions, very complex and elegant treatment options flow.

Functional medicine treatments have been described by some as “alternative” or “complementary.” As this article will demonstrate, however, the treatments are based in solid science, with ever-increasing documentation in the published, peer reviewed literature. Many treatments are directly analogous to those that are more traditionally accepted. For example, neurologists and geneticists have long provided “mitochondrial cocktails” of nutrients to support malfunctioning enzyme pathways; this is also true of the nutritional supports often provided to individuals with autism. Primary care clinicians commonly test their patients for nutritional deficiencies such as iron deficiency and guide treatments based on initial and follow-up testing; the same is true for the broad array of nutritional deficiencies seen in autism. The difference in autism is the breadth and depth of the nutritional deficiencies and biochemical inefficiencies or dysfunctions, which result in a need for a broad array of biomedical interventions.

BIOMEDICAL CONTRIBUTING FACTORS

Individuals with ASDs can have a myriad of biomedical factors that can affect brain functioning. Contributing factors may include:

- Nutritional deficiencies (particularly in zinc, magnesium, B vitamins, vitamin D, vitamin A, antioxidant nutrients, omega-3 fatty acids);
- Greater nutritional needs (eg, due to genetic mutations in biochemical pathways or poor intestinal absorption);
- Food sensitivities/intolerances;
- Opiate-like byproducts from casein and gluten;
- Altered intestinal permeability (“leaky gut”);
- Intestinal dysbiosis (insufficient beneficial bacteria, excessive yeast or Clostridia);
- Poor methylation/transsulfuration;
- Poor detoxification;
- Inflammation (of intestine and brain) and excessive pro-inflammatory cytokines;
- Oxidative stress;
- Mitochondrial/metabolic dysfunction;
- Immune imbalances/autoimmunity; and
- Insufficient oxytocin

The subset of the above factors present in any given individual varies, and the goal of the clinician is to identify the specific factors present in each patient in order to individualize treatments.

NUTRITIONAL DEFICIENCIES

Nutrition begins with intake; however, diet alone is not equivalent to nutrition. Nutrition is what an individual eats, absorbs, and delivers to the cells and what is subsequently taken up and used by the cells. Many individuals with autism have problems at the beginning of this pathway because of restricted appetites and poor intake. Poor intake can have many causes. One must always rule out medical factors such as reflux disease or constipation, neither of which is uncommon in individuals with autism. Zinc deficiency is a common contributing factor to poor/restricted appetites as it results in poor taste perception. Sensory sensitivities are very common in individuals with autism, including sensitivity to the taste, texture, smell, sight, and mixture of foods. Some individuals have very strong cravings for foods, possibly due to the creation of excess opiate-like peptides, and limit intake to those preferred foods. All of these factors combine to limit adequate intake.

Nutrients also need to be present at sufficient levels for best function to occur. Ensuring nutrients are at optimal levels, not just at bare minimum norms, can help support more optimal functioning. Certain genetic mutations, such as single nucleotide polymorphisms (SNPs), can affect an individual’s nutrient needs. For example, a subset of individuals with autism has a mutation in the methylenetetrahydrofolate reductase (MTHFR) enzyme, which confers a higher need for folate.4,5

Individuals with autism may present with a variety of nutrients at deficient or suboptimal levels.6 Blood tests and functional urine testing can help identify these deficits or inefficiencies.7

Vitamins

Unmet needs for B vitamins are common in individuals with autism. B vitamins play critical roles in human biochemistry. As a group, B vitamins support energy metabolism, neurotransmitter synthesis, fat and protein metabolism, nerve function, brain health, and overall health. Each B vitamin also has unique functions. For example, B vitamins, particularly B1, B2, and B6, are critical for optimal mitochondrial function. Mitochondrial dysfunction is common in
individuals with autism. Vitamin B6 can be helpful in a subset of individuals with autism.8 B6 is needed for numerous enzymatic reactions; the following are particularly important for individuals with autism. B6 is needed for the conversion of tryptophan to serotonin, homocysteine to glutathione, and glutamate to gamma-amino butyric acid (GABA). Folic acid and B12 play critical roles in multiple areas of function in individuals with autism. Both are needed for appropriate functioning of the methylation cycle, a pathway of critical importance especially in individuals with autism. Cerebral folate deficiency, a condition in which folic acid is not present in spinal fluid in adequate amounts, results in a number of clinical conditions, including autism.

Vitamin A deficiency also occurs in a subset of individuals with autism. Vitamin A is important for vision, including eye contact; it also has antioxidant functions. Vitamin D deficiency is common in the population as a whole and often seen in autistic individuals as well.9,10 Vitamin D is important not only for bone health but for adequate cognition and immune function.

Minerals
Zinc deficiency is common in individuals with autism.11 Zinc deficiency can be due to a number of factors, including use of antacid medications (which suppress mineral absorption), high glycemic diets, poor dietary intake of animal protein, and presence of toxic metals. Zinc is a necessary cofactor for more than 200 enzymatic reactions. It also has roles in immune function, transport of vitamin A, amino acid metabolism, metallothioneine function (important for zinc/copper regulation and toxic metal detoxification), and taste perception.

Individuals with autism often have an unmet need for magnesium. Magnesium is a necessary cofactor for more than 300 enzymatic reactions. Magnesium is necessary for adenosine triphosphate (ATP) production, neurotransmitter function, methylation, and sulfur amino acid and glutathione metabolism. Magnesium deficiency can result in many symptoms commonly seen in individuals with autism including hyperactivity, anxiety, poor sleep, and constipation.

Omega-3 Fatty Acids
Essential fatty acids are unable to be synthesized by the body and need to be taken in through diet or supplements. The standard American diet provides excessive omega-6 fatty acids, which are more pro-inflammatory, and inadequate omega-3 fatty acids. Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have numerous health benefits including anti-inflammatory effects, support of intestinal and skin health, and cognitive and vision benefits. Supplementation is usually required, as the fish sources containing the highest levels of omega-3 fatty acids are also higher in mercury.

FOOD SENSITIVITIES/INTOLERANCES
A significant subset of individuals with autism is sensitive or intolerant to foods. While some may also have traditional allergies (immunoglobulin E [IgE]-mediated), many have immunoglobulin G (IgG)-mediated sensitivities that can result in physical and/or neurological or behavioral symptoms. IgG sensitivities differ from traditional food allergies in that they can occur in a more delayed timeframe (up to 72 h after ingestion of an offending food). IgG testing can indicate an immunological reaction to a food, but the “gold standard” for diagnosis of food sensitivities is elimination of a suspected offending food for a period of time followed by a rechallenge with the food. Food-sensitive individuals will have improvement with removal of the offending food(s) and worsening with reintroduction. The most common offending foods in individuals with autism are casein, the main protein from dairy, and gluten, the main protein found in wheat and other grains.12

There are many physiological ways that foods can affect brain functioning. The most common is through the mediator of altered intestinal permeability, so-called “leaky gut.”13 Cells of the small intestine are connected by tight junctions; this prevents incompletely digested molecules from entering the circulation. When these tight junctions are disrupted (eg, due to celiac disease, insufficient essential fatty acids), incompletely digested molecules such as partially digested peptide chains from casein and gluten can enter the bloodstream. If these molecules cross the blood-brain barrier, they can then potentially affect brain function. Since neurotransmitters are peptides, it is theorized that these peptides from casein and gluten act as “false neurotransmitters” and interfere with optimum brain function. An additional challenge for a subset of individuals with autism is the creation of opiate-like peptides from casein and gluten.14-16 These opiate-like peptides are a normal step in the digestion of these foods and are broken down by the enzyme dipeptidyl peptidase IV (DPP-IV). The finding of undigested exorphin peptides in the urine is consistent with impaired or deficient activity of DPP-IV. Of interest, DPP-IV can be inactivated by mercury and organophosphates. These exorphin peptides may then also enter the circulation via a “leaky gut” with subsequent negative effects on brain functioning. Treatment options include removal of the offending foods,17-19 provision of digestive enzymes, and healing the intestinal lining to make it appropriately permeable.

Foods may be problematic in other ways. For example, cerebral folate deficiency is a condition in which folate is unable to adequately enter the cerebrospinal fluid due to the presence of blocking or binding antibodies.20,21 Casein intake can contribute to the development of folate receptor autoantibodies and a milk-free diet was shown to downregulate folate receptor autoimmunity.22 Inflammation of brain and intestine is a significant issue in individuals with autism; gluten in particular can be pro-inflammatory for many individuals.
INTESTINAL DYSBIOSIS

An ever-increasing body of research is documenting the importance of a healthy intestinal microbiome and the close interrelationship of intestinal and brain health and functioning. The intestine is home to trillions of beneficial bacteria that serve many helpful functions. These include immune support, production of nutrients (eg, biotin, vitamin K, B vitamins, short-chain fatty acids), reduction of inflammation, inhibition of the growth of potentially harmful bacteria (eg, Clostridia) and yeast, improved digestion and nutrient absorption, and reduction in allergies and skin conditions. The main risks for imbalanced intestinal flora are antibiotic use and inadequate dietary fiber. Intestinal dysbiosis, an imbalance in the beneficial organisms in the gastrointestinal tract and/or an overgrowth of pathogenic organisms, can be seen in many individuals with autism. Recent studies demonstrate that the intestinal flora of individuals with autism differs from that of individuals without autism.

When insufficient beneficial bacteria are present, pathogenic flora can overgrow, particularly Clostridia and yeast. These organisms may then secrete toxic metabolites that have several negative consequences. These toxins may contribute to the development of altered intestinal permeability and may then enter the circulation and subsequently have secondary effects on brain functioning. Toxic byproducts from Clostridia are particularly interesting. Several studies have demonstrated that injection of propionic acid (made by Clostridia) into rat brains resulted in the development of autistic-like symptoms.

Another study described negative effects from toxic metabolites (eg, propionyl-CoA) on mitochondrial energy metabolism.

METHYLATION AND TRANSSULFURATION ABNORMALITIES

The folate, methylation, and sulfation cycles are interconnected cycles that serve vital functions in purine and pyrimidine synthesis, neurotransmitter metabolism, gene expression, antioxidant support, and detoxification. These pathways often function poorly in individuals with autism. Differences in measured metabolites in these pathways and correction of the imbalances by appropriate supplementation have been well-documented in the exquisite work of S. Jill James, PhD, and others. These pathways are dependent on folic acid, vitamin B₉, and vitamin B₁₂, all of which are commonly deficient or insufficient in individuals with autism. Chronic oxidative stress, often seen in autism, also can deplete the nutrients in these pathways, further impairing their function.

DETOXIFICATION WEAKNESSES

Detoxification challenges in individuals with autism may start with something as simple as inadequate elimination due to constipation, a common coexisting medical problem. Challenges are further exacerbated by weaknesses in glutathione production as glutathione plays an important role in phase II detoxification in the liver. Glutathione is made in the transsulfuration cycle; if weaknesses exist in the folate and methylation cycles or if nutrient deficiencies are present (eg, in B₉), glutathione production is adversely affected. Abnormalities in sulfation that can affect clearance of phenols also have been documented. In the presence of these weaknesses, toxins, either internally derived or externally sourced (eg, toxic metals, organophosphates), may not be eliminated efficiently, with potentially negative consequences on brain function, mitochondrial health, etc.

MITOCHONDRIAL DISEASE OR DYSFUNCTION

While true mitochondrial disease may be seen in a small subset of individuals with autism, mitochondrial dysfunction is common. In many individuals, this is secondary to insufficient nutritional cofactors for optimum enzyme function. In addition, some individuals may have an inability to adequately synthesize certain factors (such as carnitine). Given the vital role of mitochondria for cell functioning, dysfunctions can have broad effects on overall health and well-being.

OXIDATIVE STRESS AND INFLAMMATION

Oxidative stress is a process by which the body responds to infectious or other invaders through the production of free radicals. When oxidative stress is excessive or chronic and/or when insufficient antioxidants are present, free radicals can result in damage to cell walls and to DNA. Oxidative stress also can have negative effects on the functioning of brain glial cells. Glial cells provide nourishment to neurons and clean up toxic metabolic byproducts such as glutamate. When glial cell function is poor, these functions are disrupted, with negative effects on brain function.

Increased GABA is needed to counteract the excess glutamate. When glial cell function is poor, these functions are disrupted, with negative effects on brain function. Increased GABA is needed to counteract the excess glutamate. When imbalances persist, clinical consequences can include poor language, poor sensory processing, and overall suboptimal brain function. Excessive oxidative stress has been described in autism.

Inflammation of both intestine and brain is well documented in a subset of individuals with autism. Findings analogous to inflammatory bowel disease are present in some individuals. Autopsy studies have documented low-grade chronic inflammation in the brains of individuals with autism. Inflammation is one contributing factor to excessive oxidative stress.

A more recent paradigm describes the potential negative combined effects of mitochondrial dysfunction, oxidative stress, and inflammation on brain function due to a poor “signal-to-noise” ratio. As recently described by Martha Herbert, MD, PhD, if mitochondrial function is poor, the “signals” in the brain may be of insufficient strength. With excessive oxidative stress and inflammation, background “noise” may be high. In that setting, the signals may not exceed the “noise,” and brain transmission is adversely affected.
IMMUNE IMBALANCES AND AUTOIMMUNITY

A variety of differences in the immune system have been documented in individuals with autism.44-45 A profile of increased cytokines in blood with imbalances in Th1/Th2 has been described.46 An elevated immune response also has been shown in the brains of individuals with autism, with an increase in pro-inflammatory cytokines.47 Low natural killer cell activity has been described.48 Abnormal immunoglobulin levels also may be present.49 Autoimmunity, with the presence of brain autoantibodies, such as myelin basic protein antibodies, has been described as well.50-52

THE ROLE OF OXYTOCIN

Oxytocin is primarily known for its presence in breast milk and has been referred to as the “bonding hormone.” Recent studies have shown the importance of oxytocin for social connection throughout life. Studies of high-functioning individuals with autism or Asperger’s syndrome treated with oxytocin as a nasal spray report improvements in face processing and eye contact,53 turn-taking, and emotion recognition, as well as a decrease in social anxiety. A recent study described the role of oxytocin in “signal to noise” brain filtering.54 Oxytocin strengthened some actions of fast-spiking interneurons while reducing the background activity in neighboring cells.

IMPLICATIONS FOR TREATMENT

A given individual with autism may have any combination of the above described factors, and the clinician’s challenge is to determine which factors are relevant to that individual. Once defined by clinical or laboratory evaluation, multiple potential therapeutic options become available. Treatments might include correction of nutritional deficiencies, elimination of problematic foods and/or use of digestive enzymes, restoration of optimal intestinal flora balance, support of methylation and detoxification pathways, reduction of oxidative stress and inflammation, improvement of mitochondrial function, and provision of oxytocin. By providing the body and brain with what they need and by eliminating that which may be interfering, the potential exists to significantly improve overall brain functioning and therefore quality of life for individuals with autism.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th edition (DSM-V). Arlington, VA: American Psychiatric Publishing, 2013.
2. Prevalence of autism spectrum disorders: autism and developmental disabilities monitoring network, 14 sites, United States, 2008 MMWR. http://www.cdc.gov/mmwr/pdf/ss/ss6003.pdf. Accessed October 10, 2013.
3. Schaevitz LR, Berger-Sweeney JE. Gene-environment interactions and epigenetic pathways in autism: the importance of one carbon metabolism. ILAR J. 2012;53(4):229-40.
4. Per D, Shen Y, Wu J. Association between MTHFR gene polymorphisms and the risk of autism spectrum disorders: a meta-analysis. Autism Res. 2013 May 7. doi:10.1002/aur.1300 [Epub ahead of print]
5. Paça SP, Dranca E, Kaçarç S, et al. One carbon metabolism disturbances and the C677T MTHFR gene polymorphism in children with autism spectrum disorders. J Cell Mol Med. 2009;13(10):2229-58.
6. Adams JR, Audhya T, McDonough Means S, et al. Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity. Nutr Metab (Lond). 2011;8(1):34.
7. Kaluma-Caspilnka J. Noninvasive urinary organic acid test to assess biochemical and nutritional individuality in autistic children. Clin Biochem. 2011;44(8):686-91.
8. Mousain-Bosc M, Roche M, Polge A, Pradal-Prat D, Rapin J, Bali JP. Improvement in neurobehavioral disorders in children supplemented with magnesium-vitamin B6. II. Pervasive developmental disorder autism. Magnes Res. 2010;23(4):53-62.
9. Kočovská E, Fennell E, Billstedt E, Minnis H, Gillberg C. Vitamin D and autism: clinical review. Res Dev Disabil. 2012;33(5):1541-50.
10. Mostafa GA, Al-Ayadhi LY. Reduced serum concentrations of 25-hydroxy vitamin D in children with autism: relation to autoimmunity. J Neurol Immunol. 2012 Aug 17;2013.
11. Bjorklund G. The role of zinc and copper in autism spectrum disorders. Acta Neuropathol (Wien). 2013;125(2):225-36.
12. Lau NM, Green PH, Taylor AK, et al. Markers of celiac disease and gluten sensitivity in children with autism. PLoS One. 2013 Jun 18;8(6):e66155.
13. D’Eufemia P, Celli M, Finocchiaro R, et al. Abnormal intestinal permeability in children with autism. Acta Paediatr. 1996;85(6):1076-9.
14. Reichelt KL, Trueitt D, Knisvåg AM, Brunstad G. Peptides’ role in autism with emphasis on exorphins. Microb Ecol Health Dis. 2012;23:10.3402/ mechec.v23i10.18958.
15. Reichelt KL, Knisvåg AM. Can the pathophysiology of autism be explained by the nature of the discovered urine peptides? Nutr Neurosci. 2003;6(1):29-28.
16. Reichelt KL, Knisvåg AM. The possibility and probability of a gut-to-brain connection in autism. Ann Clin Psychiatry. 2009;21(4):205-11.
17. Herbert MR, Buckley JA. Autism and dietary therapy: case report and review of the literature. J Child Neurol. 2013;28(3):375-82.
18. Whiteley P, Haracos D, Knisvåg AM, et al. The ScanBimRandomised, controlled, single-blind study of a gluten-free and casein-free dietary intervention for children with autism spectrum disorders. Nutr Neurosci. 2010;13(4):187-190.
19. Whiteley P, Shattuck P, Knisvåg AM, et al. Gluten and casein-free dietary interventions for autism spectrum conditions. Front Hum Neurosci. 2013 Jan 4;7:144.
20. Frye RE, Sequeira JM, Quadros EV, James SJ, Rossignol DA. Cerebral folate receptor autoantibodies in autism spectrum disorder. Mol Psychiatry. 2013;18(s):369-81.
21. Ramaekers VT, Blau N, Sequeira JM, Nassogne MC, Quadros EV. Folate receptor autoimmunity and cerebral folate deficiency in low-functioning autism with neurological deficits. Neuropediatrics. 2007;38(6):276-81.
22. Ramaekers VT, Sequeira JM, Blau N, Quadros EV. A milk-free diet downregulates folate receptor autoimmunity in cerebral folate deficiency syndrome. Dev Med Child Neurol. 2008;50(3):246-52.
23. Kang DW, Park JG, Ihlan ZE, et al. Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children. PLoS One. 2013;8(7):e68322.
24. Finegold SM, Moltitond S, Song Y, et al. Gastrointestinal microflora studies in late-onset autism. Clin Infect Dis. 2002 Sep 1;35(Suppl 1):S6-16.
25. Finegold SM, Dowd SE, Gontcharova V, et al. Prenatally acquired differences in fecal microflora of autistic and control children. Anaerobe. 2010;16(4):444-55.
26. Finegold SM. State of the art, microbiology in health and disease. Intestinal bacterial flora in autism. Anaerobe. 2011;17(5):268-78.
27. Shultz SR, MacFabe DF, Osenkopp KF, et al. Intracerebroventricular injection of propionic acid, an enteric bacterial metabolic end-product, impairs social behavior in the rat: implications for an animal model of autism. Neuropsychopharmacol. 2008;33(6):1115-25.
28. Shultz SR, MacFabe DF, Martin S, et al. Intracerebroventricular injections of the enteric bacterial metabolic product propionic acid inhibit cognition and sensorimotor ability in the Long-Evans rat: further development of a rodent model of autism. Behav Brain Res. 2009;200(1):133-41.
29. Swaab-MA, Sauer SW, Okun IG, et al. Secondary mitochondrial dysfunction in propionic aciduria: a pathogenic role for endogenous mitochondrial toxins. Biochem J. 2008;408(1):107-112.
30. James SJ, Cutler P, Melnyk S, et al. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr. 2004;80(6):1611-17.
31. Melnyk S, Fuchs GJ, Schulte E, et al. Metabolic imbalance associated with methylation dysregulation and oxidative damage in children with autism. J Autism Dev Disord. 2012;42(5):367-77.
32. James SJ, Melnyk S, Fuchs G, et al. Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism. Am J Clin Nutr. 2006;84(3):425-30.
33. James SJ, Melnyk S, Fuchs GJ, Schulte E, et al. Metabolic imbalance associated with methylation dysregulation and oxidative damage in children with autism. J Autism Dev Disord. 2012;42(5):367-77.
34. James SJ, Melnyk S, Fuchs G, et al. Effect of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism. Am J Clin Nutr. 2009;89(3):425-30.
35. James SJ, Rose S, Melnyk S, et al. Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism. FASEB J. 2009;23(8):2374-83.
36. Alberti A, Pirrone F, Elia M, Waring RH, Romano C. Sulphation deficit in “low functioning” autistic children: a pilot study. Biol Psychiatry.
35. Giulivi C, Zhang YF, Omana-Klusek A, et al. Mitochondrial dysfunction in autism. JAMA. 2010;304(17):2389-96.
36. Rossignol DA, Bradstreet JJ. Evidence of mitochondrial dysfunction in autism and implications for treatment. Am J Biochem Biotechnology. 2008;4(2):208-17.
37. Celestino-Soper PB, Violante S, Crawford EL, et al. A common X-linked inborn error of carnitine biosynthesis may be a risk factor for nonsyndromic autism. Proc Natl Acad Sci U S A. 2012;109(21):8274-81.
38. James SJ, Melnyk S, Jernigan S, et al. Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. Am J Med Genet B Neuropsychiatr Genet. 2008;141B(8):942-56.
39. Walker SJ, Fortunato J, Gonzalez LG, Krigsman A. Identification of a unique gene expression profile in children with regressive autism spectrum disorder (ASD) and ileocolitis. PLoS One. 2013;8(3):e58058.
40. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol. 2005;57(6):677-81.
41. Pardo CA, Vargas DL, Zimmerman AW. Immunity, neuroglia and neuroinflammation in autism. Int Rev Psychiatry. 2003;15(6):485-95.
42. Rodriguez JJ, Kern JK. Evidence of microglial activation in autism and its possible role in brain underconnectivity. Neurol Glia Biol. 2011;7(2-4):205-213.
43. Herbert MR. Autism: from how it works to how we can help more effectively. MetroDoctors: J Twin Cities Med Soc. http://plmitestsite.com/autism-from-how-it-works-to-how-we-can-help-more-effectively/. Accessed October 10, 2013.
44. Pessah IN, Seegal RF, Lein PJ, et al. Immunologic and neurodevelopmental susceptibilities of autism. Neurotoxicology. 2008;29(3):532-545.
45. Onore C, Careaga M, Ashwood P. The role of immune dysfunction in the pathophysiology of autism. Brain Behav Immun. 2012;26(3):383-92.
46. Molloy CA, Morrow AL, Meinzen-Derr J, et al. Elevated cytokine levels in children with autism spectrum disorder. J Neuroimmunol. 2006;172(1-2):198-205.
47. Li X, Chauhan A, Sheikh AM, et al. Elevated immune response in the brain of autistic patients. J Neuroimmunol. 2009;207(1-2):111-6.
48. Vojdani A, Mumper E, Granpeesheh D, et al. Low natural killer cell cytotoxic activity in autism: the role of glutathione, IL-2 and IL-15. J Neuroimmunol. 2008;196(1-2):91-94.
49. Heuer L, Ashwood P, Schauer J, et al. Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms. Autism Res. 2008;1(3):275-84.
50. Singh VK. Phenotypic expression of autoimmune autistic disorder (AAD): a major subset of autism. Ann Clin Psychiatry. 2009;21(3):148-61.
51. Singer HS, Morris CM, Williams PN, Yoon DY, Hong JJ, Zimmerman AW. Antibrain antibodies in children with autism and their unaffected siblings. J Neuroimmunol. 2006;172(1-2):149-55.
52. Cabanlit M, Wills S, Goines P, Ashwood P, Van de Water J. Brain-specific autoantibodies in the plasma of subjects with autism spectrum disorder. Ann N Y Acad Sci. 2007;1107:92-103.
53. Domes G, Heinrichs M, Kumbier E, Grossmann A, Hauenstein K, Herpertz SC. Effects of intranasal oxytocin on the neural basis of face processing in autism spectrum disorder. Biol Psychiatry. 2013;73(6):516-71.
54. Owen SJ, Tuncdemir SN, Bader FL, Tirkko N, Fishell G, Tien RW. Oxytocin enhances hippocampal spike transmission by modulating fast-spiking interneurons. Nature. 2013;500(746):31458-62.