

Article Review

THE ROLE OF SELENIUM TOWARDS DEVELOPMENT IN CHILDREN OF AUTIS SPECTRUM DISORDER (ASD)

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ABSTRACT

Autism Spectrum Disorder (ASD) is a developmental disorder, which is characterized by two symptoms, barriers to communication / social interaction and restrictive (limited) / repetitive (repetitive) behavior. Development is closely related to the nervous system, especially the cerebrum. Abnormalities in ASD children are related to the right and left hemispheres, and each hemisphere is divided into four lobes according to their function, the frontal lobes regulate behavior, language and memory. Temporal lobe to control hearing, language understanding. The parietal lobe to interpret taste (pain, temperature and touch) and the occipital lobe to interpret visual stimulation. Handling of ASD is one of them with Complementary and Alternative Medicine (CAM) biological therapy, namely selenium supplements. Selenium as an improvement in specific, non-specific, and antioxidant immune responses. Selenium as an element selenoprotein as an essential component of the enzyme glutathione peroxidase (GPx). GPx acts to reduce hydrogen peroxide (H_2O_2) to water (H_2O), improve neuronal degeneration. Selenium as an antioxidant compound, is an electron-giving compound (donor electron) and counteracts the negative effects of oxidants.

Keywords: Selenium, Development, Autism Spectrum Disorder

Introduction

ASD prevalence is increasing every year, reports from the Center for Diseases Control and Prevention (CDC) 1: 68, 2016, meaning that of 68 children, there is 1 child with ASD, whereas in 2017 it increased by 1: 36, meaning that of 36 children there is 1 children with ASD⁴. The prevalence of ASD is greater in males than females at 4:11. Autism Spectrum Disorder (ASD) is a developmental disorder, with two main symptoms namely, barriers to communication / social interaction, and restrictive (limited) / repetitive (repetitive) behavior¹. The

factors causing ASD are very complex, including genetic and non genetic factors². As for these factors, as follows:

a. Neuro inflammation and neuro immune.

In ASD there are two prominent clinical features that result from inflammation and are uncontrolled from the neuro immune system. Immune dysfunction in ASD causes an increase in behavioral response, this also causes pro-inflammatory production of cytokines to increase. Increased cytokines in ASD also indicate the severity of behavioral symptoms. Cytokines that act as pro inflammations in ASD are IL-1 β ,

IL-6 and TNF- α 11. Gastrointestinal inflammation in ASD which causes the blood brain barrier is also disrupted, due to intestinal function that provides nutrients to neurons, this can affect the work of the nervous system which is not optimal so that it triggers neuroinflammation⁵.

b. Neuropathology.

Decreased purkinje cells in the cerebellum, maturation in the limbic system which is not normal, ie decreased size of neurons, increased cell density, decreased neuropil, frontal, parietal and temporal cortex increases between 3.4% to 9%. There is a change in the size and number of cells in the diagonal nucleus of the broca, the cerebral nucleus and the inferior olive, the brain stem and neocortical malformations. On magnetic resonance imaging (MRI) in ASD, there is an increase in brain volume in ASD children 90% have greater brain volume than normal children, this causes the head circumference above average to macrocephaly. In ASD there is also a disruption in connectivity between various cortical areas in the brain, hypoactive gusus fusiformis, which functions to recognize the face²³.

c. Heavy metal poisoning.

Environmental factors greatly influence the severity of symptoms in ASD. Based on the results of research on ASD hair examination, there were concentrations of aluminum, arsenic, cadmium, mercury, lead, compared to the control group. While the Pb level did not differ significantly between ASD children and the control group²⁵. An increase in Hg concentration in the hair has a significant relationship with ASD symptoms, and conversely no significant relationship was found between other toxic metals examined in the hair with symptoms of ASD severity. There was a significant positive correlation

between lead content in ASD hair and the development of verbal communication ($p = 0.020$)²⁶.

d. Digestion

The brain and intestine have a special relationship (The Gut Brain Axis). The small intestine as the second brain, is the second nervous system after the brain, and over 60% or 2/3 of the body's entire immune system is centered in the digestive system. The small intestine is connected to the brain through neurotransmitters which also produce serotonin. Gut associated Lymphoid Tissue (GALT) is spread in the gastrointestinal mucosa²⁷. The surface of the digestive tract, especially the small intestine, is always exposed to various microbes and food. In children with ASD abnormalities occur in the intestinal flora, so that it will produce toxins, which will damage the intestinal wall, and cause holes in the intestinal wall (leaky gut). If the intestine has holes, the toxin will easily enter the blood vessels and brain, so inflammation will occur in the brain and inhibit the metabolic processes in the brain²⁴ in ASD, there is an increase in brain volume in children ASD 90% has a brain volume greater than normal children, this causes head circumference above the average to macrocephaly. In ASD there is also a disruption in connectivity between various cortical areas in the brain, hypoactive gusus fusiformis, which functions to recognize the face²³. Based on the results of the study, bacterial analysis of ASD feces, Bifidobacterium bacteria low -45%, $p = 0.002$, Enterococcus bacteria low -16%, $p = 0.05$ and high Lactobacillus bacteria + 100% $p = 0.000039$. In ASD children, proteins and peptides derived from casein and gluten cannot be digested. Peptides that cannot be accepted by the body can enter the bloodstream

and if carried to the brain will have effects such as opioids. Holes in the intestinal mucosal wall will leave opioids and other toxic substances enter the bloodstream. This toxin can damage the blood brain barrier which causes damage to consciousness, cognitive abilities, speech or behavior²⁰.

e. Genetic

At present \pm 15% ASD is associated with known genetic mutations, with differences in specific de novo or de novo gene variations. It is estimated that 37% -90% of siblings who are twins with ASD, will be at risk of ASD in their siblings¹.

f. Metabolic dysfunction

Metabolic dysfunction is mainly related to the ability to break down the components of phenolic amino acids. Amino phenolic is found in many foods as its main component can cause behavioral disorders in ASD. ASD has a low capacity to use various sulfate components so that children are unable to metabolize phenolic amino components. The phenolic amino component is the raw material for the formation of neurotransmitters, if the component is not metabolized properly there will be an accumulation of catecholamines that are toxic to the nerves. Foods that contain phenolytic amino acids: wheat (wheat), corn, sugar, chocolate, bananas and apples¹².

Result

ASD therapy

The principle of therapy in ASD with the methylation cycle. The methylation cycle is biochemical processes that help regulate regulation for attention, focusing, awareness, language development, detoxification, sleep cycle, immune support, and others. The methylation cycle in ASD therapy is a key application of homocysteine to methionine.

The production of methionine and amino acids for protein conversion which will affect the heart, blood vessels, muscle tissue, immune system and nerves. Increased synthasein synthase activity can increase methylation. In trans sulfuration it involves the conversion of homocysteine into 2 amino acids: 1) Taurine for the heart, liver, detoxification, bile acid formation and cholesterol excretion. 2) Cysteine: a direct influence on the production of glutathione peroxidase as an antioxidant strong and protection against DNA / RNA damage, heavy metal detoxification and immune support³¹.

Selenium

Selenium is a component of the amino acid selenosistein and selenometionin. Selenoprotein is the basis for assisting brain development, which is connected with redox control, prevention and oxidative repair of brain cell tissue. The role of GPx in redox regulation as selenoenzimzim as antioxidants that work to reduce oxidants¹⁴.

1. Selenium as an antioxidant

Selenium acts as the antioxidant enzyme glutathione peroxidase (GPx), where GPx acts to reduce the oxidants of hydrogen peroxide to water. Chemically, antioxidant compounds are electron-giving compounds (donor electrons). Biologically, the definition of antioxidants is compounds that can counteract or reduce the negative effects of oxidants. Antioxidants work by donating one electron to compounds that are oxidant so that the activity of these oxidant compounds can be inhibited. Antioxidants are needed by the body to protect the body from free radical attack. Impaired balance between oxidants and antioxidants caused by reactive oxygen species (ROS). There are three types of ROS, namely superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl (OH^-). The cell produces one antioxidant, namely glutathione peroxidase¹⁴.

Antioxidants improve the increase in brain neurochemistry (Brain growth factor) in ASD. Increased neurochemical excess in

neurotrophin and neuropeptides of the brain (brain - derived neurotrophic factor, neurotrophin-4, vasoactive intestinal peptide, calcitonin-related gene peptide) which is a brain chemical to regulate nerve cell addition, migration, differentiation, growth, and development of interwoven tissues neuron. In ASD there is an increase in brain growth factors and a reduction in purkinje (the site of nerve cells resulting from sensory processing and nerve impulses) in the cerebellum, reduced purkinje stimulates the growth of axons, glia (supporting tissues in the central nervous system), and myelin so that brain growth does not occur normal. In ASD there is an enlargement of the frontal lobes, causing disturbances in intellectual processes, language and motor skills. The hippocampus is abnormal (the front part of the cerebrum that plays a role in sublime function and memory processes). The amygdala is abnormal (the front side of the cerebrum that plays a role in the memory process). Parietal lobe is abnormal, resulting in no response to the environment. Abnormal limbic system that functions to control aggression and emotions³⁴. With the work of antioxidants to inhibit stress oxidative due to reactive oxygen species (ROS), then abnormalities in the ASD brain can be corrected²³.

2. Selenium as an immune system

Selenium increases the body's immune status, with double blind in 36 patients, 17 leukemia patients, and 19 solid tumor patients, Group 1 received selenium supplement, group 2 received placebo for 30 days, after that group 1 was given placebo and group 2 was given selenium supplement during 30 days, with the result: in the solid tumor an increase in neutrophyl after given selenium supplement $p = 0.0192$, Ig A and Ig G significantly increased in tumor solites compared to leukemia $p = 0.0051$ and $p = 0.0055$, Ig A increased in production after being given selenium supplements in the solit tumor group compared to leukemia $p = 0.001117$.

Based on a critical review, selenium supplements also improve brain health, prevent cancer, anti-inflammatory, control mood, reduce the risk of stroke and repair

DNA damage. Selenium supplements as well as anti-virus and selenium-dependent iodothyronine deiodinases (DIOS), are involved in the synthesis of the active thyroid hormone, triiodo-thyronine (T3), while GPx-3 protects thyroid cells from hydrogen peroxide. Based on a journal review, selenium is nonmetallic, absorption through the diet is very effective in the form of selenomethionin or selenocystein²⁰.

Biological activation of proteins, important for the GPx enzyme. GPx 1 and GPx 4 depend on selenium, which contains 4 selenocysteine residues, found in body tissues especially in the liver, kidneys and red blood cells. GPx 2 is found in the digestive tract and liver. GPx 3 is found in plasma (extacellular), kidneys and thyroid glands. GPx 70% in the cytosol, 30% in the mitochondria³⁵.

The function of GPx: a) GPx-1 to detoxify peroxide in cellular cytosol, b) GPx-2 works in the liver cytosol and digestive system tissue, c) GPx-3 as extra cellular, synthesized mainly by the kidneys, secreted to plasma to be transported to tissues others, d) GPx-4 to prevent oxidative lipid damage in the brain and other tissues³⁶.

Conclusion

Selenium is a component of the amino acid selenosistein and selenometionin. Selenoprotein is the basis for assisting brain development, which is connected with redox control, prevention and oxidative repair of brain cell tissue. The role of GPx in redox regulation as selenoenzim as antioxidants and increased immunity, which works to reduce oxidants in the improvement of brain neurochemistry (Brain growth factor) in ASD. Increased neurochemical excess in neurotrophin and neuropeptides of the brain (brain-derived neurotrophic factor, neurotrophin-4, vasoactive intestinal peptide, calcitonin-related gene peptide) which are brain chemicals to regulate nerve cell addition, migration,

differentiation, growth, and development of interwoven tissues neuron.

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