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CAUSES SYMPTOMS OF AUTISM SPECTRUM DISORDER: THEIR ATTENUATION BY A MICRONUTRIENT MIXTURE, PROBIOTICS WITH PREBIOTICS, COLLAGEN PEPTIDES, OMEGA-3, DIGESTIVE ENZYMES, AND CANNABIDIOL (CBD)

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ABSTRACT

Autism spectrum disorder (ASD) is a group of complex brain development disorders which include autism and Asperger's syndrome (AS). The prevalence of ASD was 3.2% among children aged 8 years, and it was higher among boys (4.92%) than girls (1.43%). It was higher among children of black Americans, Asian/Pacific Islanders. Native Indian, and Alaska natives than white Americans. Although genetic causes of ASD are certain; however, the impact of environmental factors and drug use during pregnancy remain uncertain. Therefore, no prevention plan for ASD can be developed at this time. The annual national cost of ASD was $41.8 billion. Since the symptoms of ASD and their causes are well defined, we have proposed an effective plan to improve current treatments of symptoms. Causes of symptoms of ASD include increased oxidative stress, chronic inflammation, elevation of glutamate and reduction in GABA levels, deficiency of serotonin and dopamine. Other internal stressors which participate in the development and maintenance of ASD symptoms include intestinal dysbiosis, dysfunctional onega-3, deficiency of gut generated GLP-1 due to increase activity of enzyme DPP-4 that degrades GLP-1, and digestive enzymes. We suggest consuming daily proposed micronutrient mixture which would simultaneously reduce oxidative stress and chronic inflammation, CBD which would reduce glutamate level and incases GABA level, and restore serotonin and dopamine levels, probiotics with prebiotics which would reverse the harmful effects of intestinal dysbiosis on the symptoms, Omeg-3 which would replace dysfunctional omega-3, Collagen peptides which have Amla and white tea extracts that have inhibitors of the enzyme DPP-4 which degrades GLP-1 and thereby maintain high level of GLP-1, and digestive enzyme to restore normal level of digestive enzymes.

KEYWORDS: Autism; oxidative stress; chronic inflammation; micronutrients; serotonin; glutamate.

1. INTRODUCTION

Autism spectrum disorder (ASD) is a group of complex brain development disorders which include autism and Asperger's syndrome (AS). In 2024 CDC reports that prevalence of ASD in the USA was 3.2% among children aged 8 years. The prevalence was higher among boys (4.92%) than girls (1.43%). It was higher among children of black Americans, Asian/Pacific Islanders. Native Indian, and Alaska natives than white Americans.

Although genetic causes of ASD are certain; however, the impact of environmental factors and drug use during pregnancy remain uncertain. Therefore, no prevention plan for ASD can be developed at this time.

2. COST OF MANAGEMENT OF ASD

In the USA in 2024, the incremental lifetime cost was estimated to be $ 2.65 million for individuals without intellectual disability, and it was $4.61 million for those with intellectual disability. The annual national cost of ASD was $41.8 billion. ASD places a considerable financial burden on families and healthcare systems.

Since the symptoms of ASD are well defined. Hence, it is possible to develop an effective plan to improve

current treatments of symptoms. To achieve this, it is essential to identify internal stressors that contribute to the development and maintenance of symptoms. It is equally important to know structural changes in the brain and their association with the symptoms of ASD.

This review presents structural changes in the brain of ASD patients and their association with certain symptoms. This review also describes causes of symptoms of ASD and their attenuation by a micronutrient mixture, probiotics with prebiotics, digestive enzymes, collagen peptides, omega-3, and cannabidiol (CBD).

3. BRAIN PATHOLOGY

Brain pathology in individuals with Autism Spectrum Disorder (ASD) includes altered brain structure, such as regional volume changes and abnormalities in neuron size and density, and impaired connectivity. These differences are linked to core symptoms like social and communication difficulties (linked to areas like the frontal lobe and amygdala) and repetitive behaviors (associated with the frontal lobe, cerebellum, and striatal circuitry). Other findings include synaptic dysfunction, impaired autophagy, and potential mitochondrial dysfunction.[1,2] The information on changes in the brain of ASD patients is also derived from the Internet. These alterations in the brain are described here.

3.1. Altered brain structures and cellular defects: Some studies report a reduced number of neurons in certain areas like the hippocampus, while others show an increased number of neurons in the prefrontal cortex.

3.2. Altered neuron size and orientation: There are findings of reduced neuron size, increased neuron density, and abnormally oriented pyramidal neurons in some areas.

3.3. Dendritic abnormalities: Impairments in the development of dendrites and a reduced number of dendritic spines are associated with ASD.

3.4. Cellular and subcellular changes: A postmortem study found smaller cell size and increased cell density in the hippocampus, limbic system, and amygdala.

3.5. Impaired autophagy: Autophagy, a process for clearing damaged proteins, is impaired in some cases of ASD, leading to synaptic deficits and behavioral issues.

4. ALTERED BRAIN CONNECTIVITY

4.1. White matter abnormalities: Some studies show a reduction in white matter and altered axonal density, suggesting impaired communication between brain regions.

4.2. Long-range connectivity: Alterations in long-range connectivity between different brain regions have been observed.

5. SYNAPTIC DYSFUNCTION

There is evidence of a reduced number of synapses in the brains of individuals with ASD which is associated with the symptoms of ASD.

6. SOCIAL AND COMMUNICATION DIFFICULTIES

Abnormalities in the frontal lobe (e.g., thickness, sulcal depth) are linked to social impairments.
Structural variations in the orbitofrontal cortex are associated with social cognition, self-regulation, and social-emotional behaviors.
Deficits in the amygdala, orbitofrontal cortex, and temporoparietal cortex are thought to drive social difficulties.

7. REPETITIVE BEHAVIORS

Changes in the frontal lobe are associated with repetitive behaviors.
Aberrant frontal-striatal circuitry is linked to repetitive movements.
Impaired cerebellar development is also associated with repetitive behaviors.

8. SYMPTOMS OF ASD

The symptoms of ASD are generally milder than those observed in patients with autism.
The major symptoms include difficulty in speech and communication, sensory and mental awareness, social interaction, and behaviour.[3] To develop an effective strategy to improve the management of autism, it is essential to know cellular defects that participate in the development and progression of symptoms of autism. Generally, children show symptoms of autism within the first year of life.

8.1. Social communication and interaction: People with autism spectrum disorder may have problems getting along with others and communicating. They may have a mixture of these and other symptoms which include following:
Does not respond to their name.
Does not want to be cuddled or held and prefer to play alone.
Have poor eye contact and show no expression on their faces.
Does not speak or lose the ability to say words or sentences as they could before.
Cannot start a conversation.
Repeat words or phrases but don't know how to use them.
Don't seem to understand simple questions or directions.
Don't show emotions or feelings.
Are passive, aggressive or disruptive when interacting with others.
Make the same movement repeatedly, such as rocking, spinning or hand-flapping.
Do activities that could hurt themselves, such as biting or head-banging.

As some children with autism spectrum disorder grow older they interact more with others and show fewer disturbances in behavior. While some with the least severe problems, eventually may lead typical or nearly typical lives, others continue to have trouble with language or social skills. And the teenage years can bring more behavioral and emotional challenges.

9. CAUSES OF SYMPTOMS OF ASD

9.1. Increased oxidative stress and chronic inflammation: Increased levels of oxidative stress, chronic neuroinflammation participates in the development and progression of autism.[3] Neurological activation and neuroinflammation occur in the brain of patient with autism.[4] In addition, inflammation contributes to the symptoms of ASD[5], Therefore, antioxidants which reduce oxidative stress and inflammation have been studied in animal models, using single agent at a time. These antioxidants including resveratrol[6-8], N-acetylcysteine[9,10], curcumin[11], and docosahexaenoic acid (DHA), a part of omega 3.[12] These studies show that antioxidants may be useful in the treatment of ASD. Indeed, human studies show that resveratrol[13], coenzyme Q10[14], NAC[15], DHA[16], omega 3[17], produce some beneficial effects in patients with ASD.

10. Limitations of Using a Single Antioxidant for Reducing Oxidative Stress and Chronic Inflammation in ASD

Most clinical studies were performed to evaluate the role of individual antioxidant in reducing the symptoms of ASD and produced inconsistent.

A few potential reasons for the failure of a single antioxidant to yield consistent beneficial effects in patients with ASD are described here.

(a) ASD patients have an elevated level of oxidative environment. Supplemented single antioxidant in such an environment would be oxidized which then would act as a pro-oxidant rather than as an antioxidant.

(b) Different antioxidants are distributed differently and in different amounts in the subcellular compartments of the cells. Supplemented single antioxidant cannot accumulate in all subcellular parts of the cell in sufficient amounts to provide an adequate protection against oxidative damage.

(c) Elevation of both antioxidant enzymes and dietary and endogenous antioxidant compounds is essential to attenuate simultaneously oxidative stress and chronic inflammation because they act by different mechanisms. Antioxidant compounds neutralize free radicals by donating electrons to those molecules with unpaired electrons, whereas antioxidant enzymes remove hydrogen peroxide (H2O2) by catalysis, converting them to water and oxygen. Supplementation with a single antioxidant alone cannot achieve this goal.

(d) Supplementation with a single antioxidant cannot protect molecules against oxidative damage in both the aqueous and lipid environment of the cells.

11.0. Requirements of Micronutrient Mixture which Can Simultaneously Elevate the Levels of Antioxidant Enzymes and Antioxidant Compounds

The failure of individual antioxidant to produce consistent benefits led us to develop a micronutrient mixture which can elevate the levels of antioxidant enzymes and dietary and endogenous antioxidant compounds at the same time. Previously we suggested that the levels of antioxidant enzymes and antioxidant compounds should be simultaneously elevated to decrease oxidative stress and inflammation at the same time.[18] Oral administration of the proposed mixture of micronutrients would enhance the levels of antioxidant compounds; however, it was not certain whether it can elevate the levels of antioxidant enzymes which requires an activation of Nrf2. The process of activation of Nrf2 and its role in enhancing antioxidant enzymes is briefly described here.

11.1. ROS-induced Activation of Nrf2: Under normal physiological conditions, ROS (reactive oxygen species) is essential to activate Nrf2. Activated Nrf2 dissociates itself from Keap1-CuI-Rbx1 complex in the cytoplasm and then migrates to the nucleus where it heterodimerizes with a small Maf protein and binds with ARE (antioxidant response element) leading to increased transcription of genes coding for several enzymes including antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase.[19-21]

11.2. Presence of Nrf2 in ASD and its activation: Nrf2 becomes dysfunctional in ASD.[22] Elevated oxidative stress is observed in ASD patients because of dysfunctional Nrf2 which was not activated by normal activator Reactive Oxygen Species (ROS). The importance of Nrf2 activation was demonstrated in several neurological diseases including ASD.[23] Antioxidants such as turmeric[24], resveratrol[25], quercetin[26,27], and green tea extract[28] activate dysfunctional Nrf2 in several diseases. It is likely these antioxidants may also activate dysfunctional Nrf2 in ASD. Proposed micronutrient mixture has these antioxidants which can elevate both antioxidant enzymes by activating dysfunctional Nrf2 as well as antioxidant compounds.

10. Ingredients of Proposed Micronutrient Mixture

This micronutrient mixture contains vitamin A (retinyl palmitate), vitamin E (both d- alpha-tocopherol acetate and d-alpha-tocopheryl succinate), natural mixed carotenoids, vitamin C (calcium ascorbate), vitamin D3, all B-vitamins, coenzyme Q10, alpha-lipoic acid, N-acetylcysteine (NAC), resveratrol, curcumin, quercetin, green tea extract, and minerals selenium and zinc. This micronutrient mixture has no iron, copper, manganese, or heavy metals. This mixture has been tested clinically for its effectiveness in reducing oxidative stress and chronic inflammation. This micronutrient mixture would simultaneously attenuate oxidative stress and chronic inflammation by enhancing the levels of antioxidant

enzymes through activation of the Nrf2 pathway as well as the levels of dietary and endogenous antioxidant compounds.[29]

11. Increased Level of Glutamate and Decreased Level of GABA in ASD

In addition to increased oxidative stress and neuroinflammation, excessive release of glutamate and reduced level of gamma-aminobutyric acid (GABA) are responsible for hyperactivity in patients with autism.[3] Antioxidant such as glutathione treatment prevents the damaging effect of glutamate in brain tissue.[30,31] Administration of CBD reduces short-term and long-term release of glutamate after traumatic brain injury.[32] CBD enhances GABA transmission.[33] These effects of CBD on glutamate and GABA can reduce hyperactivity symptom in patient with ASD. CBD also reduces oxidative stress and neuroinflammation.

12. Deficiency of Serotonin and Dopamine in the Brain of ASD patients

Children with autism have reduced capacity of synthesizing serotonin in the brain.[34] The adult patients with autism have lower binding of the serotonin transporter particularly in brain regions associated with social cognition[35,36] Low serotonin is linked to increased repetitive behaviors, irritability, and anxiety in individuals with autism.[37,38]

Dopamine plays a key role in executive functions like planning and flexible thinking, which are often altered in patients with autism.[39] Alterations in the dopamine system may explain some of these executive deficits.[40,41] Studies in genetic model of mice with autism show reduced dopamine release, which can impact motivation and learning.[42]

13. Role of CBD in the Treatment of ASD

CBD treatment induced marked to moderate improvement in 84% of ASD patients, slight improvement if 6% of cases and no improvement in 9 % of cases.[43] CBD mediates its effect via CB1R and CB2R receptors. CB1R is primarily located in the brain while CB2R is primarily expresses in the immune cells.[44] Treatment of CBD markedly reduce some symptoms of ADS among children and adolescents.[45] CBD treatment also helps treatment resistant behavior symptoms among children with ASD.[46] It improves symptoms of autism among boys.[47]

14. Restoring Serotonin Level by FDA Approved Drugs in the Treatment of ASD

FDA approved Selective Serotonin Re-uptake Inhibitors (SSRIs) such as citalopram, escitalopram, fluoxetine, fluvoxamine, and sertraline have been studied in autism spectrum disorders. Most studies demonstrate significant improvement in global functioning and in symptoms associated with anxiety and repetitive behaviors. Side-effects were mild; however, increased activation and agitation occur in some children with autism.[48]

15. Restoring Serotonin and Dopamine Levels by CBD in Patients with ASD

Treatment with cannabidiol improve treatment of anxiety, depression, and psychotic disorders.[49] This is due to the fact that CBD acts as a agonist of serotonin receptor enhancing the synthesis of serotonin while a few studies suggest that CBD acts as an inhibitor of serotonin re-uptake.[50,51] CBD also acts as a partial agonist of dopamine D2 receptor to increase the synthesis of dopamine that antipsychotic effects and reduces anxiety and depression.[52]

16. Other Internal Stressors that Contribute to the Symptoms of ASD

They include intestinal dysbiosis, dysfunctional onega-3, deficiency of gut generated GLP-1, digestive enzymes, and serotonin. They are described here.

16.1. Intestinal dysbiosis: Intestinal dysbiosis (increase in the number of harmful bacteria and decline in the number of beneficial bacteria) which produces several toxic chemicals including pro-inflammatory cytokines, impairs gut permeability that contributes to the leaky gut and immune dysfunction, and they are linked with autism.[53,54] Intestinal dysbiosis also releases pro-inflammatory cytokines including chemokine, and pro-inflammatory cytokines such as interleukin-1(IL-1B), (IL-6), interferon-gamma (INF-gamma), and tumor necrosis factor-alpha (TNF-alpha) which crosses blood brain barrier (BBB) and damage developing brain structures and connections.[55,56] Probiotics supplementation improved the symptoms of autism.[57,58] High fat maternal diet induced autism in mice which was cured by supplementation with Lactobacillus reuteri.[59] Supplementation with probiotics increases the levels of serotonin, and thereby, improved symptoms of ASD.[60]

16.2. Dysfunctional Omega-3 fatty acids (omega-3): Omega-3 plays an important role in the management of autism. It changes the composition of bacteria in the gut in favor of beneficial bacteria and reduces the release of proinflammatory cytokines. Deficiency in omega-3 may occur due to poor absorption of omega -3 from the damaged gut of patients with ASD. Omeg-3 is easily oxidized by increase oxidative stress and become dysfunctional. Supplementation with omega-3 may replace dysfunctional omega-3 and may improve hyperactivity, lethargy, and stereotypy in children with ASD.[61,62]

16.3. Deficiency of hormone GLP-1: Reduction in the level of gut-generated hormone secretin, also called GLP-1 (glucagon-like peptide-1) induces poor social interaction.[63] As a matter of fact, knockout of gene for secretin causes social interaction deficits in mice.[64] The lack of social interaction is one of the major symptoms of autism. Supplementation with collagen peptides which has Amla extract and white tea extract that contain inhibitor of enzyme dipeptidyl-peptidase-4 (DPP-4), and thereby maintain high levels of GLP-1.[65] Collagen

deficiency can occur in patients with autism because of malabsorption of protein. Deficiency of collagen may alter structural integrity of the brain that would interfere with its proper functioning.

16.4. Deficiency Digestive enzymes: Gastrointestinal dysfunction such as constipation, diarrhea, and abdominal pain is present in children with ASD.[66] Children with ASD have impaired capacity to digest protein. This was evidenced by the observation in which patients with ASD had elevated levels of urinary peptides of dietary origin.[67,68] Undigested proteins induced intestinal dysbiosis.[69] To reduce the symptoms of gastrointestinal dysfunction supplementation with probiotics has been effective in children with autism.[58] Supplementation with the digestive enzymes improved social interaction in 90% of cases and reduced hyperactivity in 80% of cases.[70]

17. CONCLUSIONS

Autism spectrum disorder (ASD) is a group of complex brain development disorders which include autism and Asperger's syndrome (AS). Genetic causes of ASD are certain. It is uncertain whether environmental factors and drug use during pregnancy causes ASD. Therefore, it is not possible to develop an effective prevention plan for ASD at this time. The major causes of symptoms of ASD include internal stressors such as increased oxidative stress, chronic inflammation, elevation of glutamate and reduction in GABA levels, deficiency of serotonin and dopamine. Other internal stressors which participate in the development and maintenance of ASD symptoms include intestinal dysbiosis, dysfunctional onega-3, deficiency of gut generated GLP-1 due to increase activity of enzyme DPP-4 that degrades GLP-1, and digestive enzymes. To improve the symptoms of ASD it is essential to reduce the impact of all internal stressors. Therefore, we suggest consuming daily proposed micronutrient mixture which would simultaneously reduce oxidative stress and chronic inflammation, CBD which would reduce glutamate level and increase GABA level, and restore serotonin and dopamine levels, probiotics with prebiotics which would reverse the harmful effects of intestinal dysbiosis on the symptoms, omeg-3 which would replace dysfunctional omega-3, collagen peptides which contain Amla and white tea extracts that have inhibitors of the enzyme DPP-4 which degrades GLP-1 and thereby maintain high level of GLP-1 that would allow flow of insulin from the pancreas to the blood, and digestive enzyme to restore normal level of digestive enzymes to ensure proper absorption of all micronutrients.

DECLARATION

Ethical statement. Since it is a review manuscript, ethical statement is not needed. Any ethical statement related to a review paper has been met.

Conflict: The author is Chief Scientific Officer of Engage Global of Utah. This company sells nutritional products to consumers.

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