Role of Environment, Nutrition, Microbiota, Mammalian Target of Rapamycin and Dietary Supplements in Autism

Khadiga S. Ibrahim a, Eman M. Elsayed b, Heba Mahdy-Abdallah *

a Environmental & Occupational Medicine Dept, National Research Centre, El-Bohouth St. (Tahrir St. Prev.) Dokki, Cairo, Egypt
b Nutrition and Food Science Dept, National Research Centre, El-Bohouth St. (Tahrir St. Prev.) Dokki, Cairo, Egypt

Abstract
Autism Spectrum Disorder (ASD) is a developmental disorder with the age of onset under 3 years old. It is characterized by definite impairments in social interactions, speech abnormalities, and stereotyped patterns of behaviors. Although the exact pathology and etiology of ASD are not fully elucidated, exposure to environmental toxins, micronutrients deficiency, dysbiosis and mutation in genes of mammalian target of rapamycin (mTOR) signaling pathway are emerging as risk factors for ASD. Maternal exposure to heavy metals, air pollutants, and pesticides markedly increases the risk of ASD. Many clinical and experimental trials documented that gastrointestinal symptoms and disturbances of the gut microbiota usually accompanied cerebral disorders in autistic patients. Furthermore, studies showed that gene mutations causing hyperactivation of mTOR significantly lead to autistic symptoms. Pharmacological and nutritional interventions revealed a significant improvement in autistic individuals. The use of dietary supplements and the elimination diets exhibit minor or no adverse effects as compared to conventional drugs. In this review article, we tried to summarize some of the etiological factors that predispose to autism. We discussed the possible mechanisms that potentiate autistic symptoms by such factors. Also, we focused on the role of interventions either by various dietary supplements or by elimination diets in the management of autism.

1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition with age of onset under 3 years old. It is estimated that 1 in 160 children worldwide suffers from ASD. This estimate represents an average figure, and reported prevalence varies substantially across studies. The prevalence of ASD in many low- and middle-income countries is so far unknown (WHO, 2018). Based on epidemiological studies conducted over the past 50 years, the prevalence of ASD appears to be increasing globally. The disease affects males more than females (4:1), however, in girls the symptoms may be more intensified (Rapin 1999; Solomon et al., 2012). ASD is characterized by a noticeable impairment of social interaction, delayed usage of language and behavioral disturbances such as self-injurious behavior (Minshawi et al., 2014). Besides, the behavioral impairment, autistic patients have marked prevalence of gastrointestinal (GI) disease and dysbiosis (White, 2003; Hsiao, 2014; Li et al., 2017), autoimmune disease (Keil et al., 2010) and mental retardation (Noterdaeme and Wriedt, 2010).

The etiology of autism is not clear, although various genetic, environmental, metabolic, neurologic and immunologic factors are probably involved. Environmental factors such as exposure to some toxic chemicals (heavy metals, pesticides, persistent and nonpersistent organic pollutants) can lead to neurological disorders (Saghazadeh and Rezaei, 2017; Voorhees et al., 2017; Guo et al., 2018 b; Jeddi et al., 2016) respectively. Early diagnosis and treatment for autistic patients exactly appear to improve their outcomes like a decreased need for special education and an increase in their independence (Elder et al., 2017). Pharmacological, behavioral and nutritional interventions have been identified to minimize symptoms in autistic children (Fung et al., 2016; Cekici and Sanliy, 2019). Meanwhile, the GI disturbances, intestinal mucosal abnormalities and altered intestinal microbiome (Fulceri et al., 2016; Li et al., 2017) extremely potentiate dietary intervention together with minimal or no side effects. Adequate nutrition ensures normal central nervous system development and a diet rich in certain nutrients like omega 3 fatty acids keep mental function (Lyall et al., 2014). Besides, adequate nutrients and nutrition have been documented to be essential in regulating molecular mechanisms that maintain synaptic function and plasticity (Maynard and Mantini, 2017). Moreover, cell proliferation, hormones and neurotransmitters’ metabolism, and deoxyribonucleic acid (DNA) synthesis in the brain noticeably depend on sufficient nutrients (Onaolapo and Onaolapo, 2018). Previous studies have indicated that protein malnutrition and deficiencies of iron and iodine in early life predispose children to compromised growth and cognition (Dosman et al., 2007). In this context, Fujisawa et al. (2016) found a strong correlation between malnutrition and autism.

*Corresponding author: hebanahdy91@gmail.com

https://doi.org/10.36547/ae.2020.2.4.79-88
Ornay et al. (2015) agreed with Fujiwara, they reported that obese mothers are liable to have autistic offsprings. On the other hand, specific maternal nutritional deficiencies are associated with increased ASD in their offsprings (Surén et al., 2013). Additionally, experimental studies have demonstrated that pregnancy is a vulnerable stage for potential neurodevelopmental deficits. Nutritional deficiencies are particularly increased during pregnancy and raises the potentiality of genetic and/or developmental impairments (Kalkbrenner et al., 2010; Neal et al., 2010). It is obvious that exposure to air pollution and its components, both in the prenatal period and in early postnatal life, has been linked to poor developmental outcomes. Kalkbrenner et al. (2014) and Karimi et al. (2017) stated that some environmental exposures are associated with autism, especially traffic-related air pollutants, some metals, and several pesticides, with suggestive trends for some volatile organic compounds (e.g., methylene chloride, trichloroethylene, and styrene) and phthalates. They also concluded that other chemicals could not be ruled out. Jeddi et al. (2016) found a significant association between phthalate exposure and risk of ASD, whereas Brown et al. (2018) found no association between polychlorinated biphenyls (PCB) and risk of ASD. Heavy metals are recognized as neurodevelopmental toxins which can lead to neurological defects, developmental delays, learning disabilities and behavioral abnormalities (Gorini et al., 2014). Mortazavi et al. (2016) introduced the hypothesis that maternal exposure to electromagnetic fields increases the release of mercury from dental amalgam fillings. They suggested that such a rise in the level of mercury may be a possible mechanism for high rates of autism in offsprings. Blood levels of mercury, arsenic, cadmium, and lead has been investigated in one hundred eighty unrelated children with ASD and 184 healthy controls (Li et al., 2018). Data showed that the children with ASD had significantly (p < 0.001) higher levels of mercury and arsenic and a lower level of cadmium. The levels of lead did not differ significantly between the groups. The results of this study are consistent with several previous studies, supporting an important role for heavy metal exposure, particularly mercury, in the etiology of ASD (Telbott et al., 2015; McCaulley, 2019). This could be explained by the possibility that increased cadmium exposure accumulates in the brain, and that cadmium is present at higher levels in mercury, arsenic, and other heavy metals. Consequently, they may pass potentially toxic metals to their fetuses or into infants during nursing. Molecular mechanisms by which metals trigger neurobehavioral disorders and, specifically, ASDs are still not completely clear. In general, some environmental factors or perinatal complications might cause a pro-inflammatory state and oxidative damage in the brain and subsequently lead to alterations in neural growth and development (Goines and Ashwood, 2013). High body burden of toxic metals in autistic patients is associated with oxidative stress and increased levels of the ratio of glutathione disulfide (GSSG) to glutathione (GSH) (Adams et al., 2011). Glutathione-S-transferase (GST) genes and enzymes play a major role in detoxification of several heavy metals. A recent systematic review suggested gender-related differences in the susceptibility to metals, with boys generally more susceptible than girls (Llop et al., 2013). Metals such as lead, mercury, and cadmium have the ability to interfere with physiological thyroid hormone levels (Chen et al., 2013). The interaction of metals with hormones and neurotransmitters may represent one of the neurotoxicity mechanisms involved in ASDs (Hall and Kelley, 2014). Kinney et al. (2010) reported that some environmental factors such as certain toxins and vitamin D deficiency increase the risk of a gene mutation that in turn can lead to an increased risk of ASD. Moreover, other environmental factors interact directly with neurotransmitter pathways. For example, lead disrupts the activity of N-methyl-D-aspartate receptors (Neal et al., 2010). More work is mandatory to estimate the effect of various chemicals and xenobiotics on the occurrence of ASD. Exposure to harmful environmental factors can alter the expression of developmental key genes in critical periods of embryo formation and raises the potentiality of genomic imprinting diseases such as autism (Karimi et al., 2017). None of the environmental factors alone are sufficient to induce autism, but rather a collection of them can be involved in the incidence of autism (Kim and Leventhal, 2015).

Nutritional Factors

The role of nutrition in ASD etiology begins as early as the prenatal period. Maternal nutrients deficiency has been strongly associated with increased risk of schizophrenia, neural tube defects and many neurodevelopmental disorders (Furuse et al., 2017). Nutritional deficiencies are particularly increased during gestation due to elevated metabolic needs imposed by the fetus, placenta, and maternal tissues and have proven to influence fetal brain development in terms of function and structure. Therefore, a pregnant woman’s diet could affect brain development which may increase autism risk. However, relatively few studies have been dedicated to understanding how maternal dietary factors could influence offspring brain development. Schmidt et al. (2011) suggested strong protection of prenatal high levels of folic acid from autism. Moreover, the risk of autistic disorder was 40% lower among those whose mothers administered folic acid supplements, 6 weeks before and after conception (Surén et al., 2013). Also, it was proven that pregnant women who are obese or suffering from diabetes may give birth to an autistic child (Connolly et al., 2016).

Maternal fish intake may also be important for ASD, as a source of essential fatty acids and vitamin D. Children of mothers with increased intake of omega 3 fatty acids before and during pregnancy had reduced risk of ASD relative to children of

2. Materials and Methods

PubMed database was used for the collection of data for the study in 2019. No limitation for the publication period was considered. Keywords were selected from the Medical Subject Headings and combined as "Autism Spectrum Disorder", "environmental factors", "nutritional factors", "microbiota", "mTOR", "dietary supplements" and "elimination diets".

Etiology of ASD

Environmental Factors

Recently, environmental factors have been involved in the etiology of ASD. There is an increasing growth in studies associating with environmental factors with ASD. Maternal environmental and or occupational exposures or both are non-genetic factors that may act during the prenatal period and cause neurodevelopmental deficits among which ASD has been introduced. Prenatal exposure to ambient air pollutants has been associated with the risk of ASD (Gong et al., 2017). Residence in the proximity of areas with high levels of air pollutants emitted from industrial processes, biogenic sources, vehicular exhaust, and combustion products increases maternal risk of giving birth to an autistic child (Weisskopf et al., 2015). It is obvious that exposure to air pollution and its components, both in the prenatal period and in early postnatal life, has been linked to poor developmental outcomes. Kalkbrenner et al. (2014) and Karimi et al. (2017) stated that some environmental exposures are associated with autism, especially traffic-related air pollutants, some metals, and several pesticides, with suggestive trends for some volatile organic compounds (e.g., methylene chloride, trichloroethylene, and styrene) and phthalates. They also concluded that other chemicals could not be ruled out. Jeddi et al. (2016) found a significant association between phthalate exposure and risk of ASD, whereas Brown et al. (2018) found no association between polychlorinated biphenyls (PCB) and risk of ASD. Heavy metals are recognized as neurodevelopmental toxins which can lead to neurological defects, developmental delays, learning disabilities and behavioral abnormalities (Gorini et al., 2014). Mortazavi et al. (2016) introduced the hypothesis that maternal exposure to electromagnetic fields increases the release of mercury from dental amalgam fillings. They suggested that such a rise in the level of mercury may be a possible mechanism for high rates of autism in offsprings. Blood levels of mercury, arsenic, cadmium, and lead has been investigated in one hundred eighty unrelated children with ASD and 184 healthy controls (Li et al., 2018). Data showed that the children with ASD had significantly (p < 0.001) higher levels of mercury and arsenic and a lower level of cadmium. The levels of lead did not differ significantly between the groups. The results of this study are consistent with several previous studies, supporting an important role for heavy metal exposure, particularly mercury, in the etiology of ASD (Telbott et al., 2015; McCaulley, 2019). This could be explained by the possibility that increased cadmium exposure accumulates in the brain, and that cadmium is present at higher levels in mercury, arsenic, and other heavy metals. Consequently, they may pass potentially toxic metals to their fetuses or into infants during nursing. Molecular mechanisms by which metals trigger neurobehavioral disorders and, specifically, ASDs are still not completely clear. In general, some environmental factors or perinatal complications might cause a pro-inflammatory state and oxidative damage in the brain and subsequently lead to alterations in neural growth and development (Goines and Ashwood, 2013). High body burden of toxic metals in autistic patients is associated with oxidative stress and increased levels of the ratio of glutathione disulfide (GSSG) to glutathione (GSH) (Adams et al., 2011). Glutathione-S-transferase (GST) genes and enzymes play a major role in detoxification of several heavy metals. A recent systematic review suggested gender-related differences in the susceptibility to metals, with boys generally more susceptible than girls (Llop et al., 2013). Metals such as lead, mercury, and cadmium have the ability to interfere with physiological thyroid hormone levels (Chen et al., 2013). The interaction of metals with hormones and neurotransmitters may represent one of the neurotoxicity mechanisms involved in ASDs (Hall and Kelley, 2014). Kinney et al. (2010) reported that some environmental factors such as certain toxins and vitamin D deficiency increase the risk of a gene mutation that in turn can lead to an increased risk of ASD. Moreover, other environmental factors interact directly with neurotransmitter pathways. For example, lead disrupts the activity of N-methyl-D-aspartate receptors (Neal et al., 2010). More work is mandatory to estimate the effect of various chemicals and xenobiotics on the occurrence of ASD. Exposure to harmful environmental factors can alter the expression of developmental key genes in critical periods of embryo formation and raises the potentiality of genomic imprinting diseases such as autism (Karimi et al., 2017). None of the environmental factors alone are sufficient to induce autism, but rather a collection of them can be involved in the incidence of autism (Kim and Leventhal, 2015).
mothers of low intakes of omega 3 fatty acids (Lyall et al., 2014). In contrast, Lyall et al. (2013) found no association between prenatal fish oil and ASD. Low maternal and fetal vitamin D levels have been proven as a risk for ASD (Ali et al., 2019). Vitamin D insufficiency in mothers has been linked to impaired language skills in their children at ages 5-10 years (Whitehouse et al., 2013). Vitamin D influences neuronal differentiation, metabolism of neurotrophic factors and neurotoxins, protection from brain inflammation, endocrine function and fetal brain growth. Also, vitamin D can decrease the risk of viral infection for pregnant woman. Infectious disease during pregnancy adversely influences brain development that may lead to autism. Vitamin D level is important, especially in the third trimester of pregnancy when the fetal brain develops (Larqué et al., 2018). Thus, vitamin D supplementation during pregnancy can confer protection against autism either directly or indirectly by aiding proper brain development and enhancing the immune system, respectively. Moreover, during the perinatal period, maternal diet plays a crucial role in the maturation of the vital organs and neuronal connections. If nutrition is deficient of specific micro or macronutrients or overloaded with excess calories, many developmental disorders can be devastating and long-acting because the brain is especially sensitive to prenatal nutrition. Autism is hypothesized to be attributed in part to such factors that may date back to very early life (Moody et al., 2017).

The gut microbiota

The human gut contains up to 100 trillion micro-organisms including different species of bacteria. Bacteroidetes and Firmicutes phyla are the most predominant bacterial species in the human microbiota (Eckburg et al., 2005). Although the exact etiology and pathology of autism still not obvious, gut-brain interactions have received certain attention. There is a complex bidirectional axis between the gut microbiota and the brain (Liu et al., 2019). Communication along this axis principally shows how signals from gut microbiota affect brain function, and on the other hand, brain messages influence microbiota activity and other GI functions. This bidirectional communication is mainly achieved through neuroendocrine and neuroimmune mechanisms (Mayer, 2011). In autistic patients characteristic neurological deficits are generally associated with various GI symptoms (Adams et al., 2011). It was documented that in ASD, the intestinal inflammation is often accompanied by elevated neuroinflammatory markers and reduced serotonin levels in the brain (de Theije et al., 2014). Such deficits and symptoms may be initiated from dysbiosis or microbial imbalance which could disturb the coordination of the gut microbiota-brain axis (Pulikkan et al., 2019). Metagenomic analysis proved that autistics have a decrease in Bacteroidetes, an elevation in the ratio of Firmicutes to Bacteroidetes, and an increase in Betaproteobacteria (Parracho et al., 2005). Moreover, Clostridia, Bacteroidetes, and Desulfovibrio are common bacteria that may promote GI symptoms and neurological autistic behaviors (MacFabe, 2012). They not only modulate the intestinal immune system but also produce certain metabolites that contribute directly to autism pathology. For instance, Clostridium produces a potent neurotoxin that manifests a wide variety of behavioral deficits seen in autism (Bolte, 1998). Besides, it’s another metabolite, 3-hydroxyphenyl-3-hydroxy propionic acid (BHPHA) depletes catecholamines in the brain, consequently, genus Clostridium is strongly correlated with the etiology of autism (Kesli et al., 2014). Generally, the colonization of gut microbiota commences at the time of birth on exposure to vaginal microbiota. The host genomic significantly influences microbiota activity and diversity. Also, environmental factors that include, infections, diet, stress, diseases and antibiotics may alter microbiota natural composition (Nicholson et al., 2012). Additionally, adult maternal immune activation results in fetuses that have ASD features, dysbiosis in gut microbiota and an altered blood metabolome profile (Hsiao et al., 2013). Besides, recent studies have documented that probiotics and prebiotics administration may be an effective therapy for autistics via modulation gut microbiota (Parracho et al., 2010; Liu et al., 2016) respectively.

The mammalian (mechanistic) target of rapamycin (mTOR)

ASD exhibited aberrant expression of various genes, but those involved in the mTOR signaling pathway like Neurofibromatosis type 1 (NF1), Tuberculous sclerosis proteins 1 and 2 (TSC1, TSC2), Phosphatase and Tensin homologue (PTEN), and Fragile X mental retardation protein (FMRP) are the most associated with autism. Single gene mutations result in enhanced mTOR activity in the brain of the ASD model (Ehninger and Silva, 2009). Consequently, an increase in the phosphorylation of proteins is observed with concomitant elevation of neuroglins that participate in the formation and maintenance of synapses between neurons. This caused an increased synaptic excitation/inhibition ratio which may be a risk for ASD (Wang and Doering, 2013). Additionally, the mTOR-signaling pathway has a potential role in directing the immune responses. Kim et al. (2008) proved that mTOR complex1 (mTORC1) when activated in mast cells results in survival, differentiation and cytokine production. Moreover, mTOR activation is shown to markedly attenuate autophagy (Yu et al., 2010) in the intestine that is essential to limit intestinal inflammation. Therefore, a loss of both immune regulation and intestinal barrier integrity resulted from mTOR hyperactivity, thus, in ASD distribution of the mTOR signaling pathway could disrupt immune response, gastrointestinal tract, and brain. By this way, mTOR signaling in ASD may be considered as an important factor in the gut-immune-brain axis (Van Sadelhoff et al., 2019). Therapeutic strategies for autism could manage the signaling pathway. Kotajima-Murakami et al. (2019) documented that pharmacological treatment by rapamycin successfully recovered mutations in the expression of some mTOR genes with consequence improvement in social communication in the ASD model. However, intervention with some nutrients like amino acid may manipulate the mTOR signaling pathway with minor or no adverse effects. They are capable to inhibit mTOR, inflammation, improve gut barrier function and normalize microbiota composition and immunity in the ASD patients (Van Sadelhoff et al., 2019). Interestingly, cellular levels of different amino acids are maintained through the mTOR signaling pathway and the disturbance of this pathway significantly dysregulates amino acids that is strongly associated with autism (Maynard and Manzini, 2017; Smith et al., 2019).

Nutritional assessment of autistic patients

Several studies have high lightened that individuals with autism are nutritionally vulnerable because they have a picky eating pattern and sensory sensitivity; both predispose them to restricted dietary intakes (Emond et al., 2010). Nutritional assessment includes dietary, anthropometric and biochemical evaluations for autistic patients. In addition, clinical examination that assesses the patients for signs which are consistent with nutrient deficiencies. Finally, the environmental factors assessments that affect the nutritional status, such as socioeconomic status and lifestyle (Ranjan and Nasser, 2015).
Dietary measurements

They include both qualitative and quantitative assessments of dietary intake which could determine adequacies and inadequacies inpatient nutrient intake. Consequently, nutritional status can be evaluated. The majority of autistic children exhibited nutritional challenges that include difficulty accepting new foods, late acceptance of solid food, restricted intake of food based on its color, texture, appearance etc, meal time presentations difficulties like position of food on a plate or even the type of plate, increased sensory sensitivity, disruptive mealtime behaviors such as not eating with family, eating the same foods and refusing the change and finally, the pica behavior. Autistic children are called picky eaters; however, this habit does not correlate with a lack of appetite (Williams et al., 2000). They more frequently accept food of low texture and highly energetic and particularly refuse vegetables. Although they eat less variety of foods, their total calories, carbohydrates or fat intakes are not statistically different as compared with normally developing children (Emond et al., 2010) indicating that their satiety mechanisms are not impaired. Their protein intake is approximately similar to normal children, but the nondairy protein intake was increased in ASDs children (Zimmer et al., 2012). Therefore, it is obviously clear that macronutrient deficiencies are often not present in children with autism (Herndon et al., 2009). Besides, a substantial number of autistic children had inadequate intakes of calcium, zinc, iron, and vitamins; D, C, E, riboflavin, B12, and folie acid and choline, which may be attributed to less consumption of vegetables, fruits and salads with concomitant reduction of these essential micronutrients (Bandini et al., 2010). In the contrary vitamin B6 intake was found to be significantly higher in autistic children than typically developing children. However, deficiencies of micronutrients in autistic children could be overcome by giving those fortified foods rather than additional vitamins or food supplements.

Anthropometric measurements

Anthropometric assessments include height, body mass index (BMI) and head circumference (HC). Early recognition of such measurements will serve as a noninvasive, inexpensive, and objective method of nutritional status evaluation. Such measurements have been carried out with autistic children and compared them with typically developing controls. An early warning signal of vulnerability to autism may be an abnormally accelerated rate of growth (Courchesne et al., 2001). This growth abnormality may be attributed to nonspecific expression of biological abnormalities that are present in these disorders. There are inconsistent results in the prevalence of obesity in autistic children. Some studies reported an overweight or obesity prevalence in ASD patients, which was similar to nonautistic children (Curtin et al., 2010). Other studies found a higher prevalence of obesity in autistic children than controls (Egan et al., 2013) which may be explained by their unusual dietary patterns that are accompanied by decreased access to appropriate physical activity. Concerning HC, studies showed that autistic children have an atypical head growth pattern that is at birth, they have a normal HC, followed by an increase in the rate of growth of HC until one year of age. Then, there is a rapid decrease in HC between 12 and 24 months, which is normal as compared with controls (Redei and Courchesne, 2006). Many authors have postulated that this abnormally accelerated growth in HC is attributed to dysregulation of growth in general. The relation between HC and height is inconsistent. Some studies stated that HC is relatively increased in comparison with height (Grandgeorge et al., 2013), others reported that HC is normal (Mraz et al., 2007) or smaller (Schrieken et al. 2013) relative to height.

Biochemical measurements

Estimations of nutrients and nutrient-related substances in biological specimens are important in the diagnosis of autism before the clinical signs or symptoms are apparent. Besides, the obtained knowledge of this analysis helps to determine the treatment plan and monitor its effectiveness. Autistic children have decreased concentrations nearly below the reference range of folate and vitamin B12 (Ali et al., 2011), pantothenic acid, biotin and vitamin E (Adams et al., 2011) and vitamin D (Meguid et al. 2010). Meanwhile, vitamin B6 has an elevated and broad distribution in autistic children that is very fascinating. The highest concentration of vitamin B6 may be explained by a low activity of pyridoxal kinase that converts pyridoxal and pyridoxine into the active form pyridoxal 5-phosphate (PSP). Compared with controls, autistic children have lower concentrations of lithium, calcium, magnesium (Adams et al., 2011), iodine and chromium (Adams et al., 2006) and selenium (Lakshmi Priya and Geetha, 2011). The significant correlation between vitamin D (25-hydroxyvitamin D) and calcium supports the idea that autism is a vitamin D deficiency disease (Meguid et al., 2010). By contrast, copper, phosphorus, and boron were elevated in autistic children (Adams et al., 2011; Ranjan and Nasser, 2015) and also mercury and lead. On the other hand, the prevalence of iron deficiency and anemia in ASD patients is reported (Bilgic et al., 2010). However, iron deficiency results in impaired cognition and developmental defects which could further compromise their behavior and communication. Concerning amino and fatty acids, autistic children have lower levels of plasma tyrosine and tryptophan (Adams et al., 2011) which may impair serotonin synthesis that has an important role in the neurogenesis and also in neurotransmission. The contributory factors to such decreased amino acid levels may be decreased protein intake or digestion by autistic children. Autistic patients have elevated glutamate levels in plasma (Aldred et al., 2003) that may be closely related to the behavioral changes in autism. Moreover, omega 3 polyunsaturated fatty acid concentration is significantly lower in children with autism (El-Ansary et al., 2011).

Dietary interventions

Dietary intervention mostly includes either: Dietary supplements or Elimination diets or both together (Adams et al., 2018; Fraguas et al., 2019). Successful dietary interventions could quickly relieve the autistic symptoms and are usually used as complementary with conventional pharmacological drugs.

Dietary supplements

Folic acid and vitaminB12 supplements

Both folic acid and B12 participate in the methionine cycle that involves the regeneration of methionine through the transfer of the methyl group from 5-methyltetrahydrofolate. Methionine forms S- adenosylmethionine (SAM) which is the primary methyl donor for DNA, Ribonucleic acid (RNA), phospholipids, proteins, and neurotransmitters. Another important role for the methionine cycle is the production of glutathione, a crucial antioxidant compound. Vitamin B12 and folic acid deficiencies were seen in many autistic children (Ali et al. 2011). Moreover, patients with autism exhibited cerebrospinal fluid (CSF) deficiency of folic acid that may be attributed to the action of serum antibodies against folate receptors. These antibodies bind folic acid receptors with
concomitant inhibition of folic acid synthesis and reduction level in CSF (Ramaekers et al., 2005). In this view, Mckee et al. (2017) pointed out that dietary methyl donor supplementation in early life can change cognitive performance and motivation. Meanwhile, vitamin B₁₂ deficiency may result from a digestive cause, especially rare assumption of animal sources. Pineles et al. (2010) demonstrated reversible optic nerve neuropathy in autistic patients via vitamin B₁₂ replenishment. Hence early detection of folic acid and vitamin B₁₂ deficiencies may be an essential contributory factor in preventing ASD or in determining the therapeutic interventions for autistic ones. Also, a diet rich in these nutrients or supplements may be supportive of pharmacotherapy.

**Vitamin C Supplement**

Vitamin C is essential for the synthesis of neurotransmitters and via its antioxidant power, it protects the brain and nervous tissue against free radicals. Planerova et al. (2017) demonstrated that ASD patients may have scurvy, which results from vitamin C deficiency which was a consequence of typical food consumption by those patients. Malhi et al. (2017) agreed with the previous authors in that ASD children failed to achieve vitamin C requirements. Moreover, moderate doses of vitamin C with other vitamins may affect sleep disorders and gastrointestinal troubles in ASD patients (Adams and Holloway, 2004). Besides, vitamin C supplementation in an autistic patient with normal or low serum vitamin C level, may exhibit a positive impact concerning the pathological behavior through prevention of dysregulation of glutamatergic signaling of the brain, consequently, reducing brain inflammation (Blaylock and Strunecka, 2009). Vitamin C could be complementary to conventional therapy taking into consideration its tolerance in autistic patients, therefore, continuous monitoring is essential.

**Vitamin B₆ supplement**

Dietary vitamin B₆ supplements were proven to improve behavior in autistic children (Martineau et al. 1985). Moreover, Wong and Smith (2006) demonstrated that no marked benefits of vitamin B₆ administration in ASD children. However, vitamin B₆ has an essential role in CNS as it participates in neurotransmitter synthesis like serotonin, dopamine, and epinephrine which may be altered in autistic children. Therefore, vitamin B₆ supplementation could be beneficial for autistic patients, taking into consideration to adjust its doses because high blood levels are accompanied by low activities of both kinase and oxidase enzymes that transform vitamin B₆ to the active form PSP.

**Vitamin A and D supplements**

Many autistic patients have vision problems besides other behavioral and clinical symptoms. Hence, the administration of vitamin A may be helpful (Uyanik, 2006). In agreement with the previous author, Megson (2000) demonstrated that vitamin A supplement is effective in reducing autistic symptoms since there was an absence of specific genes in ASD patients encoding an essential protein for vitamin A synthesis. Moreover, Guo et al. (2018a) proposed that vitamin A supplementation may improve symptoms and reduce 5-hydroxytryptamine (5-HT) levels in autistic children. Hence, vitamin A supplementation is a rational therapy for children with autism. Concerning vitamin D, it was proven that adequate intake of this vitamin from a diet or as a supplement may reduce the risk of autism by providing the proper development of the brain and immune system. It also has a neuroprotective effect and influence many neurotransmitter interactions (Meguid et al., 2010). Jia et al. (2015) concluded that vitamin D₃ may play a significant role in the etiology of ASD. In this context, Feng et al. (2017) reported that autistic children exhibit clinical improvement after vitamin D₃ supplementation. While Kerley et al. (2017) reported that vitamin D supplementation did not affect the primary outcome with limited and incompatible effects in children with ASD. This may be attributed to vitamin D activity and dose.

**Probiotics supplement**

Autistic patients frequently suffered from several gastrointestinal disturbances like diarrhea, constipation, and inflammation. Therefore, the use of probiotics may be beneficial as they help to restore the normal intestinal microflora and normal intestinal epithelial cells, consequently reducing gastrointestinal disturbances. Moreover, probiotics could increase the utilization of food ingredients and vitamin synthesis by the body that may be helpful for autistic patients who have multiple nutrient deficiencies. Besides, probiotics enhance immunity and inhibit many pathogens developments (Galdeano et al., 2019). Probiotics are also supposed to improve intestinal permeability, enhance the attainment of a balanced intestinal microflora, and alter the mucosal immune response (Critchfield et al., 2011).

**Mineral supplement**

Disturbed cognitive function and concentration, mood changes, and slow growth may be associated with iron deficiency in autistic children. In addition, decreased serum iron levels can cause sleep and nervous system disorders which were significantly improved with oral iron supplements (Dosman et al., 2007). Also, autistic patients appear to be at risk for zinc (Zn) deficiency (Sweetman et al., 2019). Copper (Cu) toxicity and have low Zn/Cu ratio that predisposes the body to oxidative stress. Hence, zinc supplementation is required treatment for autism (Isaacson et al. 1996). Taking into consideration that it is important to estimate and follow the levels for both Cu and Zn together during Zn therapy because these two trace elements are antagonistic in function, and essential for living cells (Bjorklund, 2013). Moreover, selenium deficiency was documented in autistic children (El-Ansary et al., 2017) therefore, it should be supplied.

**Amino acid supplement**

Amino acids play a crucial role in the brain as they are precursors to neurotransmitters or they behave as neurotransmitters themselves. Serotonin plays essential role in both brain and intestinal development. Since the brain-gut axis disturbances are a major complication in autistic children; serotonin may modulate these changes (Margolis, 2017). Tryptophan supplementation potentiates the production of serotonin. Taurine has antioxidant properties and is associated with improved visual symptoms. Also, L-carnosine has been shown to improve vocabulary, total score and behavior in autistic children (Chez et al., 2002). It is obvious that the neurotransmitter imbalance in the central nervous system (CNS) could participate in autism pathophysiology. There was an increase in glutamate levels in autistic children as a result of upregulation of glutaminergic gene expression. In this concern, the oral administration of N-acetylcysteine exerts an anti-glutaminic effect besides its antioxidant power through glutathione production (Dean et al., 2011). Besides, the aforementioned potential role on mTOR that exerted by many amino acids.
Polyunsaturated fatty acids (PUFA) supplement

Phospholipids in the brain and retina are rich in PUFA, especially n-3 PUFA such as docosahexaenoic (DHA). DHA converted to eicosapentaenoic acid (EPA) by 15-lipoxygenase. Oxylipins could regulate cell redox homeostasis and neurotransmitters signaling pathways. There is evidence that inadequate consumption of maternal DHA may be a risk of impaired CNS function. Also, DHA intake above the nutritional requirement may modify the risk of many CNS diseases (Sun et al., 2017). It was found that ASD populations have decreased DHA levels and, hence, n-3PUFA supplementation can noticeably improve ASD symptoms (Mazahery et al., 2017). In contrast, Politi et al. (2008) observed no significant improvement of disease severity and frequency, after omega-3 supplementation in adult patients with ASD. On the contrary, Cheng et al. (2017) suggest that supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and stereotypy in ASD patients. Also, a comprehensive nutritional and dietary intervention with DHA and eicosapentaenoic acid (EPA), vitamin A, B complex, folic acid and coenzyme Q10 for autistic children, showed a significant improvement in autism symptoms and developmental age (Adams et al., 2018). Further trials are required to explore the potential advantages of omega 3 fatty acid supplementation in ASD patients.

Elimination diets

These diets were designed to reduce or even completely remove foods or food additives in ASD patients, they include:

Gluten-free diet and/or casein-free diet

Patients with ASD have gastrointestinal tract troubles that might be due to increased intestinal permeability. Digestion of casein and gluten generates peptides that can reach the bloodstream through the leaky gut and bind to the opioid receptors, causing deleterious CNS effects (Reichelt et al., 1990). Hyman et al. (2016) do not provide evidence to document the general use of the gluten-free /casein-free diet.

Ketogenic diet

It contains high fat, low carbohydrate, and low protein concentrations consequently about 90% of energy from fat. The ketogenic diet could reduce the symptoms in the autistic patients with a significant improvement in communication ability (Evangelio et al. 2003). The ketogenic diets may improve social effect in children with ASD (Lee et al., 2018).

Specific carbohydrate diet

This diet mainly contains monosaccharides from fruits, honey or vegetables, while complex carbohydrates are limited. It is used to alleviate the malabsorption and growth of pathogenic intestinal microorganisms (Gottschall, 2004). Barnhill et al. (2020) declared at the 16-week intervention with the specific carbohydrate diet protocol was well tolerated in a 4-year-old child diagnosed with ASD and Fragile X syndrome, improving growth status, gastrointestinal symptoms, and behaviors.

Low oxalate diet

In autistic children, gastrointestinal dysfunction permits some substances like oxalate to cause abnormalities in their CNS. Autistic patients have high blood levels of oxalate about 3 fold the reference value with concomitant increased risk for ASD (Konstantynowicz et al., 2012). Therefore, the autistic patients should restrict oxalate containing food like spinach, figs and green apples.

Declaration of interest

The authors have no conflicts of interest

References

1. Adams, J. B., Audhya, T., Geis, E., Gehn, E., Fimbres, V., Pollard, E. L., Mitchell, J., Ingram, J., Hellmers, R., Laake, D., Matthews, J. S., Li, K., Naviaux, J. C., Naviaux, R. K., Adams, R. L., Coleman, D. M., Quig, D. W. 2018. Comprehensive Nutritional and Dietary Intervention for Autism Spectrum Disorder: A Randomized, Controlled 12-Month Trial. Nutrients 10(3): pii: E369. https://doi.org/10.3390/nu10030369
2. Adams, J. B., Audhya, T., Mcdonough-Means, S., Rubin, R. A., Quig, D., Geis, E. 2011. Nutritional and meta-bolic status of children with autism vs. neurotypical children, and the association with autism severity. Nutrition & Metabolism, 8: 34. https://doi.org/10.1186/1743-7075-8-34
3. Adams, J. B., Holloway, C. 2004. Pilot study of a moderate dose multivitamin/mineral supplement for children with autistic spectrum disorder. Journal of Alternative and Complementary Medicine, 10(6):1033-1039.
4. Adams, J.B., Holloway, C.E., George, F., Quig, D. 2006. Analyses of toxic metals and essential minerals in the hair of Arizona children with autism and associated conditions, and their mothers. Biological Trace Element Research, 110: 193–209. https://doi.org/10.1385/BTER:110:3:193
5. Aldred, S., Moore, K.M., Fitzgerald, M., Waring, R.H. 2003. Plasma amino acid levels in children with autism and their families. Journal of Autism and Developmental Disorders, 33: 93-97.
6. Ali, A., Vasileva, S., Langguth, M., Alexander, S., Cui, X., Whitehouse, A., Mccrath, J. J., Eyles, D. 2019. Developmental Vitamin D Deficiency Produces Behavioral Phenotypes of Relevance to Autism in an Animal Model. Nutrients, 11(5), 1187. https://doi.org/10.3390/nu11051187
7. Ali, A., Waly, M.I., Al-Farsi, Y.M., Essa, M.M., Al-Sharbatii, M.M., Deth, R.C. 2011. Hyperhomocysteinemia among Omani autistic children: a case-control study. Acta Biochimica Polonica, 58(4): 547-551.
8. Bandini, L. G., Anderson, S. E., Curtin, C., Cermak, S., Evans, E. W., Scampini, R., Maslin, M., Must, A. 2010. Food
selectivity in children with autism spectrum disorders and typically developing children. The Journal of Pediatrics, 157(2): 259-264. 

BARNHILL, K., DEVLIN, M., MORENOHT, POTTAS, A., RICHARDSON W., SCHUTTE, C., HEWITSON, L. 2020. Brief Report: Implementation of a Specific Carbohydrate Diet for a Child with Autism Spectrum Disorder and Fragile X Syndrome. Journal of autism and developmental disorders, 50(5): 1800–1808.

BILGIC, A., GURKAN, K., TURKOGLU, S., AKCA, OF, KILIC, B.G., USLU, R. 2010. Iron deficiency in preschool children with autistic spectrum disorders. Research in Autism Spectrum Disorders, 4: 639–644.

BJORKLUND, G. 2013. The role of zinc and copper in autism spectrum disorders. Acta neurobiologiae experimentalis, 73: 225–236.

BLAYLOCK, R.L., STRUNECKA, A. 2009. Immune-glutamatergic dysfunction as a central mechanism of the autism spectrum disorders. Current Medical Chemistry, 16 (2): 157-170. 

BOLTE, E.R. 1998. Autism and Cistodieniota. Medical Hypotheses, 51:133–144.

BROWN, A. S., CHESLACK-POSTAVA, K., RANTAKOKKO, P., KIVIRANTA, H., HINKKA-YLI-SALOMAKI, S., MCEAGUE, I. W., SURCEL, H. M., SOURANDER, A. 2018. Association of Maternal Insecticide Levels with Autism in Offspring from a National Birth Cohort. The American journal of psychiatry, 175(11): 1094-1100. 

https://doi.org/10.1176/appi.ajp.2018.17101129

CEKICI, H., SANLIER, N. 2019. Current nutritional approaches in managing autism spectrum disorder: A review. Nutritional Neuroscience, 22(3):145-155.

CHEN, A., KIM, S.S., CHUNG, E., DIETRICH, K.N. 2013.Thyroid hormones in relation to lead, mercury, and cadmium exposure in the National Health and Nutrition Examination Survey, 2007-2008. Environmental Health Perspectives, 121(2):181–186.

CHENG, Y. S., TSENG, P. T., CHEN, Y. W., STUBBS, B., YANG, W. C., CHEN, T. Y., WU, C. K., LIN, P. Y. 2017. Supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and stereotypy in children with autism spectrum disorders: a meta-analysis of randomized controlled trials. Neuropsychiatric disease and treatment, 13: 2531-2543. 

https://doi.org/10.2147/NDT.S147305

CHEZ, M. G., BUCHANAN, C. P., AIMONOVITCH, M. C., BECKER, M., SCHEAFFER, K., BLACK, C., KOMEN, J. 2002. Double-blind, placebo-controlled study of L-carnosine supplementation in children with autistic spectrum disorders. Journal of child psychology, 17(11), 833–837.

CONNOLLY, N., ANIXT, J., MANNING, P., PING-I LIN, D., MARSOLO, K.A., BOWERS, K. 2016. Maternal metabolic risk factors for autism spectrum disorder: An analysis of electronic medical records and linked birth data. Autism Research, 9(8): 829-837.

COURCHESNE, E., KARNS, C.M., DAVIS, H.R., ZICCARDI, R., CARPER, R.A., TIGUE, Z.D., ET AL. 2001. Unusual brain growth and linked birth data. Autism Research, 4(9): 1080.

COUTT, C., ANDERSON, S.E., MUST, A., BANDING, L. 2010.The prevalence of obesity in children with autism: a secondary data analysis using nationally representative data from the National Survey of Children's Health. BMC Pediatrics, 10: 11

DEAN, O., GIORLANDO, F., BERK, M. 2011. N-acetylaspartate in psychiatry: current therapeutic evidence and potential mechanisms of action. Journal of Psychiatry and Neuroscience, 36 (2): 78-86.

DE THEJE, C. G., WOPEREIS, H., RAMADAN, M., VAN EIJDTHOVEN, T., LAMBERT, J., KNOL, J., GARSSEN, J., KRANEVELD, A. D., OOEZER, R. 2014. Altered gut microbiota and activity in a murine model of autistic spectrum disorders. Brain, Behavior, and Immunity, 37:197–206.

DOSSMAN, C. F., BRIAN, J. A., DRMIC, I. E., SENTHILSELVAN, A., HARFORD, M. M., SMITH, R. W., SHARIEFF, W., ZLOTKIN, S. H., MOLDOFSKY, H., ROBERTS, S. W. 2007.Children with autism: effect of iron supplementation on sleep and ferritin. Pediatric neurology, 36(3): 152-158.

ECKBURG, P. B., BIK, E. M., BERNSTEIN, C. N., PURDOM, E., DETHLEFSEN, L., SARGENT, M., GILL, S. R., NELSON, K. E., RELMAN, D. A. 2005. Diversity of the human intestinal microbial flora. Science (New York, N.Y.), 308(5782): 1635–1638. 

https://doi.org/10.1126/science.1105911

EGAN, A.M., DREYER, M.L., ODAR, C.C., BECKWITH, M., GARRISON, C.B. 2013. Obesity in young children with autism spectrum disorders: prevalence and associated factors. Childhood Obesity, 9 (2):125-131.

EHNINGER, D., SILVA, A.J. 2009. Genetics and neuropsychiatric disorders: treatment during adulthood. Nature Medicine, 15,849–850. 

https://doi.org/10.1038/nm0909-849

ELS-ANSARY, A., BJORKLUND, G., TINKOV, A.A., SKALNY, A.V., AL DERA, H. 2017. Relationship between selenium, lead, and mercury in red blood cells of Saudi autistic children. Metabolic Brain Disease, 32(4): 1073-1080.

ELS-ANSARY, A. K., BACHA, A. G., AL-AAYHID, L.Y. 2011. Impaired plasma phospholipids and relative amounts of essential polyunsaturated fatty acids in autistic patients from Saudi Arabia. Lipids in health and disease, 10:63. 

https://doi.org/10.1186/1476-511X-10-63

ELS-ANSARY, A.K., BACHA, A.G., KOTB, M. 2012. Etiology of autistic features. The persisting neurotoxic effects of propionic acids. Journal of Neuroinflammation, 9:74

ELDER, J.H., KREIDER, C.M., BRASHER, S.N, ANSELL, M. 2017. Clinical impact of early diagnosis of autism on the prognosis and parent–child relationships. Psychology Research and Behavior Management, 10:283-292.

EMOND, A., EMMETT, P., STEER, C., GOLDING, J. 2010. Feeding symptoms, dietary patterns, and growth in young children with autism spectrum disorders. Pediatrics, 126(2), e337-342. 

https://doi.org/10.1542/peds.2009-2391

ESTEBAN-FIGUEROA, P., CANALS, J., FERNANDEZ-CAO, J.C., ARIJA VAL, V. 2019. Differences in food consumption and nutritional intake between children with autism Spectrum Disorders and typically developing children: A meta analysis. Autism, 23(5): 1079-1095.

EVANGELIOU, A., VLACHONIKOLIS, I., MIHALIDIOU, H., SPILOTI, M., SKARPAZEOU, A., MAKARONAS, N., PROKOPIOU, A., CHRISTODOULOU, P., LIAPI-ADAMIDOU, G., HELIDONIS, E., SBYRAKIS, S., SMEITINK, J. 2003. Application of a ketogenic diet in children with autistic behavior: pilot study. Journal of Child Neurology, 18(2): 113-118.

FENG, J., SHAN, L., DU, L., WANG, B., LI, H., WANG, W., WANG, T., DONG, H., YUE, X., XI, Z., STAAL, W. G., JIA, F. 2017. Clinical improvement following vitamin D3 supplementation in Autism Spectrum Disorder. Nutritional Neuroscience, 20(5):284-290. 

https://doi.org/10.1080/1028415X.2015.1123847

FRAGUAS, D., DÍAZ-CANEJA, C. M., PINA-CAMACHO, L., MORENO, C., DURÁN-CUTILLA, M., AYORA, M., GONZÁLEZ-VIOQUE, E., DE MATTEIS, M., HENDREN, R. L., ARANGO, C., PARELLADA, M. 2019. Dietary Interventions for Autism Spectrum Disorder: A Meta-analysis. Pediatrics, 144(5): e20183218. 

https://doi.org/10.1542/peds.2018-3218

FUJWARA, T., MORISAKI, N., HONDA, Y., SAMPEL, M., TANI, Y. 2016. Chemical, Nutrition, and antispectrum disorder: A mini-review. Frontiers in Neuroscience, 10:174. 

https://doi.org/10.3389/fnins.2016.00174

FULCERI, F., MORELLI, M., SANTOCCHI, E., CENA, H., DEL BIANCO, T., NARZISLA, S., MURATORI, F. 2016. Gastrointestinal symptoms and behavioral problems in preschoolers with Autism Spectrum Disorder. Digestive and liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver, 48(3), 248–254. 

https://doi.org/10.1016/j.dld.2015.11.026
40. FUNG, L. K., MAHAJAN, R., NOZZOLILLO, A., BERNAL, P., KRAZNER, A., JO, B., COURY, D., WHITAKER, A., VEEENSTRA-VANDERWEELE, J., HARDAN, A. Y. 2016. Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis. Pediatrics, 137(2):S124-35.

41. FURUSE, T., MIYAKE, K., KOHDA, T., KANEDA, H., HIRASAWA, T., YAMADA, I., ET AL. 2017. Protein-restricted diet during pregnancy after insemination alters behavioral phenotypes of the progeny. Genes & Nutrition, 12: 1. https://doi.org/10.1016/j.genun.2016.05-050-2

40. GOINES, P. E., ASHWOOD, P. 2013. Cytokine dysregulation in autism spectrum disorders (ASD): Possible role of the environment. Neurotoxicology and teratology, 36: 67-81. http://dx.doi.org/10.1016/j.ntt.2012.07.006

40. GONG, T., DALMAN, C., WICKS, S., DAL, H., MAGNUSSON, C., LUNDHOLM, C., ET AL. 2017. Perinatal Exposure to Traffic-Related Air Pollution and Autism Spectrum Disorders. Environmental Health Perspective, 125:119-125.

40. GORINI, F., MURATORI, F., MORALES, M.A. 2014. The Role of Heavy Metal Pollution in Neurobehavioral Disorders: A focus on Autism Rev. Journal of Autism and Developmental Disorders, 1:354-372.

40. GOTTSCHELL, E. 2004. Digestion-gut-autism connection: the Specific Carbohydrate Diet. Medical Veritas The Journal of Medical Truth 1:261-271.

40. GRANDGEORGE, M., LEMONNIER, E., JALLOT, N. 2013. Autism spectrum disorders: head circumference and body length at birth are both relative. Acta Paediatrica, 102 (9): 901-7.

40. GUO, M., ZHU, J., YANG, T., LAI, X., LIU, X., LIU, J., CHEN, J., LI, T. 2018a. Vitamin A improves the symptoms of autism spectrum disorders and decreases 5-hydroxtryptamine (5-HT): A pilot study. Brain Research Bulletin, 137: 35-40. https://doi.org/10.1016/j.brainresbull.2017.11.001

40. GUO, Z., XIE, H. Q., ZHANG, P., LOO, Y., TU, T., LIU, Y., FU, H., XU, L., VALSAMJONES, E., BOKSA, P., ZHAO, B. 2018b. Oxidos as potential risk factors for autism spectrum disorder. Environment International, 121(Pr 1), 906-915.

40. HALL, L., KELLEY, E. 2014. The contribution of epigenetics to understanding genetic factors in autism. Autism, 18(8):872-81.

40. HERNDON, A. C., DIGUISEPPI, C., JOHNSON, S. L., LEIFERMAN, J., REYNOLDS, A. 2009. Does nutritional intake differ between children with autism spectrum disorders and children with typical development? Journal of Autism and Developmental Disorder, 39(2):212-222.

40. HSIAO, E. Y., MCBRIDE, S. W., HSIEH, S., SHARON, G., HYDE, E. R., MCCUE, T., CODELLI, J. A., CHOW, J., REISMAN, S. E., PETROSTINO, J. F., PATTERTSON, P. H., MAZMANIAN, S. K. 2013. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell, 155: 1451–1463.

40. HSIAO, E.Y. 2014. Gastrointestinal Errors in Autism Spectrum Disorder. Harvard Review of Psychiatry, 22: 104-111.

40. HYMAN, S. L., STEWART, P. A., FOLEY, J., CAIN, U., PECK, R., MORRIS, D. D., WANG, H., SMITH, T. 2016. The Gluten-Free/Casein-Free Diet: A Double-Blind Challenge Trial in Children with Autism. Journal of Autism and Developmental Disorders, 46(1):205-220.

40. ISAACSON, H. R., MORAN, M.M., HALL, A., PREKOSOVICH, M.A. 1996. Autism: a retrospective outcome study of nutrient therapy. Journal of Applied Nutrition, 48:110-118.

40. JEDDI, M. Z., JANANI, L., MEMARI, A. H., AKHONDZADEH, S., YUNESIAN, M. 2016. The role of phthalate esters in autism development: A systematic review. Environmental Research,151:493-504. https://doi.org/10.1016/j.envres.2016.08.021

40. JIA, F., WANG, B., SHAN, L., XU, Z., STAAL, W.G., DU, L. 2015. Core symptoms of autism improved after vitamin D supplementation. Pediatrics, 135(1):e196-198.

40. KALKBRENNER, A.E., SCHMIDT, R.J., PENLESKY, A.C. 2014. Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence. Current Problems Pediatric and Adolescent Health Care, 44(10):277-318.

58. KARMI, P., KAMALI, E., MOUSAVI, S. M., KARAHMADI, M. 2017. Environmental factors influencing the risk of autism. Journal of research in medical sciences, 22: 27.

58. KEIL, A., DANIELS, J. L., FORSEN, U., HULTMAN, C., CNOTTINGIUS, S., SÖDERBERG, K. C., FEYCTHING, M., SPAREN, P. 2010. Parental Autoimmune Diseases Associated With Autism Spectrum Disorders in Offspring. Epidemiology, 21 (6): 805-808.

58. KERLEY, C.P., POWER, C., GALLAGHER, L., COGHLAN, D. 2017. Lack of effect of vitamin D3 supplementation in autism: a 20-week, placebo-controlled RCT. Archives of Disease in Childhood, 102(11):1030-1036.

58. KESLI, R., GOKCEN, C., BULUG, U., TERZI, Y. 2014. Investigation of the relation between anaerobic bacteria genus clostidium and lateonset autism etiology in children. Journal Immunoassay and Immunochemistry, 35:101–109.

58. KIM, M.S., KUEHN, H.S., METCALFE, D.D., GILFILLAN, A.M. 2008. Activation and function of the mtorc1 pathway in mast cells. Journal of Immunology, 180:4586–4595.

58. Kim, Y.S., Leventhall, B.L. 2015. Genetic Epidemiology and Insights into Interactive Genetic and Environmental Effects in Autism Spectrum Disorders. Biological Psychiatry, 77:66–74.

58. KINNEY, D. K., BARCH, D. H., CHAYKA, B., NAPOLEON, S., MUNIR, K. M. 2010. Environmental risk factors for autism: do they help cause de novo genetic mutations that contribute to the disorder? Medical Hypotheses, 74(1):102-106.

58. KONSTANTYNOWICZ, J., POROWSKI, T., ZOCH-ZWIERCZYK, W., TUMASIELewska, J., KADZIELA-OLECH, H., KULAK, W., OWENS, S. C., PIOTROWSKA-JASTRZEBSKA, J., KACZMARSKI, M. 2012. A potential pathogenic role of oxalate in autism. European journal of paediatric neurology. EJPN: official journal of the European Paediatric Neurology Society, 16(5): 485–491.

58. KOTAJIMA-MURAKAMI, H., KOBAYASHI, T., KASHII, H., SATO, A., HAGINO, Y., TANAKA, M., NISHITO, Y., TAKAMATSU, Y., UCHINO, S., IKEDA, K. 2019. Effects of rapamycin on social interaction deficits and gene expression in mice exposed to valproic acid in utero. Molecular brain, 12(1): 3. https://doi.org/10.1186/s13041-018-0423-2

58. LAKSHMI PRIYA, M.D., GEETHA, A. 2011. Level of trace elements (copper, zinc, magnesium and selenium) and toxic elements (lead and mercury) in the hair and nail of children with autism. Biological Trace Element Research, 142:148–158.

58. LAqué, E., MORALES, E., LEIS, R., BLANCO-CARNERO, J.E. 2018. Maternal and Foetal Health Implications of Vitamin D Status during Pregnancy. Annals of Nutrition and Metabolism, 72(3):179–192.

58. LEE, R., CORLEY, M. J., PANG, A., ARAKAKI, G., ABBOTT, L., LAKSHMI PRIYA, M.D., GEETHA, A. 2011. Level of trace elements (copper, zinc, magnesium and selenium) and trace elements (lead and mercury) in the hair and nail of children with autism. Archives of Ecotoxicology (2020) 7:151:493-504. https://doi.org/10.1016/j.envres.2020.09.009

58. LEE, R., LUNG, K., KEAT, S. 2012. Cerebral atrophy and oxidative stress in autism. Neurobiology of Disease, 48(3):283-292.

58. LEE, R., LUNG, K., KEAT, S. 2012. Cerebral atrophy and oxidative stress in autism. Neurobiology of Disease, 48(3):283-292.

58. LEE, R., LUNG, K., KEAT, S. 2012. Cerebral atrophy and oxidative stress in autism. Neurobiology of Disease, 48(3):283-292.

58. LEE, R., LUNG, K., KEAT, S. 2012. Cerebral atrophy and oxidative stress in autism. Neurobiology of Disease, 48(3):283-292.

58. LEE, R., LUNG, K., KEAT, S. 2012. Cerebral atrophy and oxidative stress in autism. Neurobiology of Disease, 48(3):283-292.
autism spectrum disorders. American Journal of Epidemiology, 178(2): 209–220.

76. LYALL, K., SCHMIDT, R.J., HERTZ-PICCIOTTO, I. 2014. Maternal lifestyle and environmental risk factors for autism spectrum disorders. International Journal of Epidemiology, 43(2): 443-468.

77. MACFAE, D.F. 2012. Short-chain fatty acid fermentation products of the gut microbiome: implications in autism spectrum disorders. Microbial Ecology in Health and Disease, 23:19260–19284.

78. MALDONADO GALDEANO, C., CAZORLA, S.I., LEMME DUMIT, J.M., ET AL. 2019. Beneficial Effects of Probiotic Consumption on the Immune System. Annals of Nutrition and Metabolism, 74(2):115-124.

79. MALHI, P., VENKATESH, L., BHARTI, B., SINGHP. 2017. Feeding Problems and Nutrient Intake in Children with and without Autism: A Comparative Study. Indian Journal of Pediatric, 84(4): 283-288.

80. MARGOLIS, K.G. 2017. A role for the serotonin reuptake transporter in the brain and intestinal features of autism spectrum disorders and developmental antidepressant exposure. Journal of Chemical Neuroanatomy, 83-84, 36-40.

81. MARTINEAU, J., BARTHELEMY, C., GARREAU, B., LELORD, G. 1985. Vitamin B6, magnesium, and combined B6-Mg: therapeutic effects in childhood autism. Biological Psychiatry, 20(5):467-478.

82. MAYER, E. A. 2011. Gut feelings: the emerging biology of gut-brain communication. Nature Reviews Neuroscience, 12: 453–466.

83. MAYNARD, T.M., MANZINI, M.C. 2017. Balancing Act: Maintaining Amino Acid Levels in the Autistic Brain. Neuron, 93 (3):476-479.

84. MAZAHERY, H., STONEHOUSE, W., DELSHAD, M., KRUGER, M.C., CONLON, C.A., BECK, K.L., VON HURST, P. 2017. Relationship between Long Chain n-3 Polyunsaturated Fatty Acids and Autism Spectrum Disorder: Systematic Review and Meta-Analysis of Case-Control and Randomised Controlled Trials. Nutrients, 19: 9(2) pii: E155.

85. MCCALULLEY, M.E. 2019. Autism spectrum disorder and mercury toxicity: use of genomic and epigenetic methods to solve the etiologic puzzle. Acta Neurobiologiae Experimentalis, 79: 113–125

86. MCKEE, S.E., GRISSOM, N.M., HERDT, C.T., & REYES, T.M. 2017. Methyl donor supplementation alters cognitive performance and motivation in female offspring from high-fat diet-fed dams. FASEB Journal, 31(6): 2352-2363.

87. MEGSON, M.N. 2000. Is autism a G-alpha protein defect reversible with natural vitamin A? Medical Hypotheses, 54(6): 979-983.

88. MEGUID, N.A., HASHISH, A.F., ANWAR,M., SIDHOM, G. 2010. Reduced serum levels of 25-hydroxy and 1,25-dihydroxy vitamin D in Egyptian children with autism. Journal of Alternative Complementary Medicine, 16: 641–645.

89. MINSHAWI, N.F., HURWITZ, S., FODSTAD, J.C., BIEBL, S., MORRIS, D.H., MCDONIGLE, C.J. 2014. The association between self-injurious behaviors and autism spectrum disorders. Psychology Research and Behavior Management, 7: 125-136.

90. MOODY, L., CHEN, H., PAN, Y.K. 2017. Early-Life Nutritional Programming of Cognition. The Fundamental Role of Epigenetic Mechanisms in Mediating the Relation between Early-Life Environment and Learning and Memory. Advances in Nutrition, 3(2):337-350.

91. MORTAZAVI, G., HAGHANI, M., RASTEGARIAN, N., ZAREL, S., MORTAZAVI, S.M.J. 2016. Increased release of Mercury from dental amalgam fillings due to maternal exposure to Electromagnetic Fields as a possible mechanism for the high rates of autism in the offspring: Introducing a Hypothesis. Journal of Biomedical Physics & Engineering, 6(1):41-46.

92. MRAZ, K.D., GREEN, J., DUMONT-MATHIEU, T., MAKIN, S., &FEIN, D. 2007. Correlates of head circumference growth in infants later diagnosed with autism spectrum disorders. Journal of Child Neurology, 22(6):700-713.

93. NEAL, A.P., STANSFIELD, K. H., WORLEY, P. F., THOMPSON, R. E., GUILARTE, T. R. 2010. Lead exposure during synaptogenesis alters vesicular proteins and impairs vesicle release: potential role of NMDA receptor-dependent BDNF signaling. Toxicological Sciences, 116(1): 249-263.

94. NICHOLSON, J. K., HOLMES, E., KINROSS, J., BURCELIN, R., GIBSON, G., JIA., W., PETTERSSON, S. 2012. Host-gut microbiota metabolic interactions. Science, 336:1262–1267.

95. NOTERDAEME, M.A., WRIEDT, E. 2010. Comorbidity in autism spectrum disorders - I. Mental retardation and psychiatric comorbidity. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, 38(4): 257-266.

96. ONAOLAPO, O.J., ONAOLAPO, A.Y. 2018. Nutrition in autism spectrum disorders: A review of evidences for an emerging central role in aetiology, expression, and management. AIMS Medical Science, 5:122-144.

97. ORNOY, A., WEINSTEIN-FUDIM, L., ERGAZ, Z. 2015. Prenatal factors associated with autism spectrum disorders (ASD). Reproductive Toxicology, 56:155-169.

98. PARRACHO, H.N., BINGHAM, M.O., GIBSON, G.R., MCCARTNEY, A.L. 2005. Differences between gut microbiota of Children With autistic spectrum disorders and that healthy children. Journal of Medical Microbiology, 54:997-991.

99. PARRACHO, H.M., GIBSON, G.R., KNOTT, F., BOSSCHER, D., KLEEREBEZEM, M., MCCARTNEY, A.L. 2010. A double-blind, placebo-controlled, crossover-designed probiotic feeding study in children diagnosed with autistic spectrum a double-blind, placebo controlled, crossover-designed probiotic feeding study in children diagnosed with autistic spectrum disorders. International Journal of Probiotic and Prebiotic, 5:69–74.

100. PINELES, S.L., AVERY, R.A., LIU, G.T. 2010. Vitamin B12 optic neuropathy in autism. Pediatrics, 126(4):e967-970.

101. PLANEROVA, A., PHILIP, S., ELAD, S. 2017. Gingival bleeding in a patient with autism spectrum disorder: A key finding leading to a diagnosis of scurvy. Quintessence International, 48(5):407-411.

102. POLITI, P., CENA, H., COMELLI, M., MARRONE, G., ALLEGRI, C., EMANUELE, E., UCELLI DI NEMI, S. 2008. Behavioral effects of omega-3 fatty acid supplementation in young adults with severe Autism: An open label study. Archives of medical research, 39 (7): 682–685.

103. PULIKKAN, J., MAZUMDER, A., GRACE, T. 2019. Role of the Gut Microbiome in Autism Spectrum Disorders. Advances in Experimental Medicine and Biology, 1118:253-269.

104. RAMAekaERS, V.T., ROTHENBERG, S.P., SEQUEIRA, J.M., OPLADEN, T., BLAU, N., QUADROS, E.V., SELHUB, J. 2005. Autoantibodies to Folate Receptors in the Cerebral Folate Deficiency Syndrome. New England Journal of Medicine, 352:1985-1991.

105. RANJAN, S., NASSER, J.A. 2015. Nutritional Status of Individuals with Autism Spectrum Disorders: Do We Know Enough? Advances in Nutrition, 6(4):397-407.

106. RAPIN, I. 1999. Autism in search of a home in the brain [Editorial]. Neurology, 52(5): 902–904. https://doi.org/10.1212/WNL.52.5.902

107. REDCAY, E., COURCHESNE, E. 2005. When Is the Brain Enlarged in Autism? A Meta-Analysis of All Brain Size Reports. Biological Psychiatry, 58:1-9.

108. REICHLERT, K.L., EKREM, J., SCOTT, H. 1990. Gluten, milk proteins and autism: dietary intervention effects on behavior and peptide secretion. Journal of Applied Nutrition, 42:1-11.

109. SAGHAZADEH, A., REZAEI, N. 2017. Systematic review and meta analysis links autism and toxic metals and highlights the impact of country development status: higher blood and erythrocyte levels for mercury and lead, and higher hair antimony, cadmium, lead, and mercury. Progress in Neuro-psychopharmacology & Biological Psychiatry, 79(Pt B): 340-368.

110. SCHMIDT, R. J., HANSEN, R. L., HARTIALA, J., ALLAYEE, H., SCHMIDT, L. C., TANCREDI, D. J., TASSONE, F., HERTZ-PICCIOTTO, I. 2011. Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism. Epidemiology (Cambridge, Mass.), 22(4):476-485.

111. SCHRIEKEN, M., VISSER, J., OOSTERLING, I., VAN STEIJN, D., BOUTELLAAR, J., DONERS, R., ROMMELSE, N. 2013. Head circumference and height abnormalities in autism revisited: the role of pre- and perinatal risk factors. European child & adolescent psychiatry, 22(1):35-43.
112. Smith, A.M., King, J.J., West, P.R., Ludwig, M.A., Donley, E., Burrier, R.E., Ami, D.G. 2019. Amino Acid Dysregulation Metabolites: Potential Biomarkers for Diagnosis and Individualized Treatment for Subtypes of Autism Spectrum Disorder. Biological Psychiatry, 85(4):345–354. https://doi.org/10.1016/j.biopsych.2018.08.016

113. Solomon, M.I., Miller, M., Taylor, S.L., Hinshaw, S.P., Carter, C.S. 2012. Autism Symptoms and Internalizing Psychopathology in Girls and Boys with Autism Spectrum Disorders. Journal of Autism and Developmental Disorders, 42(1):48-59.

114. Sun, G.Y., Simonyi, A., Fritsche, K.L., Chuang, D.Y., Hännink, M., Gu, Z., Greenleaf, C.M., Yao, J.K., Lee, J.C., Beversdorff, D.Q. 2018. Docosahexaenoic acid (DHA): An essential nutrient and a nutraceutical for brain health and diseases. Prostaglandins Leukotrienes Essential Fatty Acids, 136:3-13.

115. Suren, P., Roth, C., Bresnahan, M., Haugen, M., Hornig, M., Hirtz, D., Lie, K.K., Lipkin, W.I., Magnus, P., Reichborn-Kjellerud, T., Schjolberg, S., Davey Smith, G., Oyen, A.S., Susser, E., Stolttenberg, C. 2013. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. Jama, 309(6):570-577.

116. Sweetman, D.U., O'Donnell, S.M., Lalor, A., Grant, T., Greaney, H. 2019. Zinc and vitamin A deficiency in a cohort of children with autism spectrum disorder. Child: care, health and development, 45(3):380-386. https://doi.org/10.1111/cch.12655

117. Talbott, E.O., Marshall L.P., Rager, J.R., arena, V.C., Sharma, R.K., Stacy, S.L. 2015. Air toxics and the risk of autism spectrum disorder: the results of a population based case-control study in southwestern Pennsylvania. Environmental Health, 14: 80. https://doi.org/10.1186/s12940-015-0064-1

118. Uyanik, O., Dogangun, B., Kayaalp, L., Korkmaz, B., Derveent, A. 2006. Food faddism causing vision loss in an autistic child. Child: care, health and development, 32(5):601-602.

119. Van Sadelhoff, J., Perez Pardo, P., Wu, J., Garssen, J., Van Bergenhenegouwen, J., Hogenkamp, A., Hartog, A., Kraneveld, A.D. 2019. The Gut-Immune-Brain Axis in Autism Spectrum Disorders: A Focus on Amino Acids. Frontiers in endocrinology, 10: 247. https://doi.org/10.3389/fendo.2019.00247

120. Voorhees, J.R., Rohlman, D.S., Lein, P.J., Pieper, A.A. 2017. Neurotoxicity in preclinical models of occupational exposure to organophosphorus compounds. Frontiers in neuroscience, 10: 590. https://doi.org/10.3389/fnins.2016.00590

121. Wang, H., Doering, L.C. 2013. Reversing autism by targeting downstream mtor signaling. Frontiers in Cellular Neuroscience, 7:28.

122. Weisskopf, M.G., Kjoumourtzoglou, M.A., Roberts, A.L. 2015. Air Pollution and Autism Spectrum Disorders: Causal or Confounded? Current Environmental Health Reports, 2(4):430-439.

123. White, J.F. 2003. Intestinal Pathophysiology in Autism. The Gut: Pathophysiology in Autism Spectrum Disorders. - Association of Amino Acid Dysregulation with the Autism Phenotype among Offspring. Journal of Autism and Developmental Disorders, 43 (7): 1495-1504.

124. Williams, P.G., Dalrymple, N., Neal, J. 2000. Eating habits of children with autism. Pediatric Nursing, 26(3):259-264.

125. Wong, H.H., Smith, R.G. 2006. Patterns of complementary and alternative medical therapy use in children diagnosed with autism spectrum disorders. Journal of Autism and Developmental Disorders, 36 (7): 901-909.

126. World Health Organization (WHO). 2018. Autism spectrum disorders, Fact sheet https://www.who.int/news-room/fact-sheets/detail/autism-spectrum-disorders

127. Yu, L., McPhee, C.K., Zheng, L., Mardones, G.A., Rong, Y., Peng, J., Mi, N., Zhao, Y., Liu, Z., Wan, F., Hailey, D.W., Oorschot, V., Klumperman, J., Baehrecke, E.H., Lenardo, M.J. 2010. Termination of autophagy and reformation of lysosomes regulated by mTOR. Nature, 465:942-946. https://doi.org/10.1038/nature09076