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Potential Role of Cytokines and Vitamin D in Pathophysiology of Autism Spectrum Disorder

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Abstract: Autism spectrum disorder is a neurodevelopmental condition with a wide range of symptoms. An early stage begins before the age of 3. Autistic people have trouble socializing, communicating verbally and nonverbally, as well as having stereotypical interests and behaviors. Due to the increasing frequency of autism in children and the lack of effective treatments, it is one of the most challenging conditions to treat in psychology. Autism has a perplexing etiology. Immune regulation of neuronal proliferation, synapse formation, and plasticity are all enhanced by the chemosensory immune system. Immune responses in autistic people are aberrant, according to hundreds of studies conducted over the past four decades. Vitamin D deficiency, as well as cytokine profile and signaling abnormalities, have become increasingly prevalent in recent years and have been the focus of continuing research in the field of autism spectrum disorder. Numerous studies indicate that vitamin D plays a significant role as a neuroactive steroid that can influence neuronal development, axonal connections, and brain structure and function. In addition, vitamin D insufficiency during pregnancy is associated with a number of negative effects on the fetus. Immune abnormalities have previously been identified, and the role of cytokines in these abnormalities is highlighted in this review, which aims to determine whether cytokines are useful as potential biomarkers that may participate in the development of disease. The purpose of this review is to outline the function of the immune system and to examine the relationship between the immune biomarkers, cytokines with as emphasis on the role of vitamin D as an immune regulator.

Keywords: Autism spectrum disorder, autism severity, pathogenesis, vitamin D, immune abnormality, neurodevelopmental disorder, cytokines.

Introduction:

A series of neurodevelopmental problems known as autism spectrum disorders are characterized by difficulties in social communication, restricted and repetitive patterns of behavior, and selective attention (1,2). Leo Kanner used the term "autism" in 1943 to describe a condition that impairs the social and emotional development of young children. ASD affects 1 in 160 children globally, according to the World Health Organization (3,4). Autism is generally acknowledged as a "spectrum" disorder that can manifest in a variety of psychological, neurological, and cognitive abnormalities (5,6). Some evidence indicates that environmental and genetic factors may contribute to the etiology of ASD. However, the molecular mechanisms behind these conditions are not well known, and there are no specific treatments (7).

Young brains are far more metabolically active than adult brains and account for approximately 60 % of the body's overall energy usage (8). Early healthy nutrition is essential for neurodevelopment (9.10). During crucial periods, shortages in proteins, fatty acids, various types of minerals, and vitamins (including vitamins A, D, B6, B9, and B12) may have a negative effect on brain function owing to the role that these nutrients play in signaling cascades that alter neuronal functional ability (8, 9, 11). On the basis of epidemiological studies, it has been postulated that vitamin D deficiency enhances the incidence of ASD (12). The relationship between vitamin D and autism emerged when evidence of a greater prevalence of autism in children living in areas with fewer ultraviolet-B rays than those living in sunny areas increased (12).

Vitamin D is converted to its active form, 1,25(OH)D (calcitriol), by two hydroxylation mechanisms in the liver and kidneys (13). In the early stages of brain development and growth, calcitriol acts as a

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neuroactive hormone that regulates a number of different processes (9, 12, 14). Neurotransmission and proliferation of brain cells are two ways in which vitamin D is thought to affect neurodevelopment (14, 15). In addition, vitamin D is crucial for the regulation of the inflammatory system because it controls the creation of immune cells and inflammatory cytokines, both of which are necessary for the pathogenesis of many immune-related problems (16). Strong inflammatory states are linked to ASD due to the connection between high inflammatory cytokines and cognitive impairment (12). Compared to healthy children, people with ASD had much higher levels of the cytokines interleukin (IL)-1, IL-6, IL-8, interferon-gamma (IFN-γ), and monocyte chemotactic-1 proteins (MCP-1) and much lower levels of the cytokine transforming growth factor-1 (17).

The history of autism is exceedingly complex. It has altered drastically during the past few years. The term "autism" was coined by Swiss-German psychiatrist Eugen Bleuler in 1908 to describe children with signs of severe schizophrenia and unconscious imagination. Since then, the diagnosis, classification, and meaning of autism have all changed dramatically (18). In the 1940s, Leo Kanner and Hans Asperger coined the term "autistic" to describe children with the specific features. Leo Kanner, a psychiatrist at Johns Hopkins University, proposed the word "autism" in 1943 when he diagnosed autistic as a separate neurological disease with no known etiology. Around this time, Kanner coined the term "early infantile autism" and afterwards referred to Kanner syndrome (19). Hans Asperger and Kanner exhibited comparable impairments in communication, social interaction, and a wide variety of symptoms. In 1981, the term "Asperger's syndrome" was made public, referring to a disease previously defined by Hans Asperger (20).

Clinically, autism spectrum disorder is diagnosed based on the presence of several essential characteristics, including delayed social development, repetitive behaviors and interests, delayed speech development, and learning impairment. They typically do not initiate interactions with their surroundings, especially social ones. They often have trouble understanding information and coordinating their activities, and they may have ritualized or rigid ways of acting (21).

Since the first autism survey conducted in England by Lotter in 1966, the quantity and sophistication of epidemiological surveys have expanded (22). During the previous two decades, the prevalence of ASD has grown rapidly. In 2000, the Centers for Disease Control and Prevention (CDC) projected that one in every 150 children had ASD. The frequency of ASD increased from 1 in 110 children in 2006 to 1 in 88 children in 2008. In 2012, the Autism and Developmental Disabilities Monitoring Network revised its ASD prevalence estimates to one in every 68 children. (23).

In 2020, CDC stated that around one in every 54 children in the United States had been diagnosed with an ASD (3). ASDs may significantly limit the capacity of an individual to conduct daily activities and participate in society. This ratio is thought to be the same across all racial, ethnic, and socioeconomic backgrounds, although gender variations exist. The prevalence of ASD appears to be four to five times higher in boys than in girls (23). The steady increase in the prevalence of autism ASD may have been contributed to in part by more careful screening for disease in children and adults, as well as improved diagnostic criteria and more accurate behavioral and neuropsychological scales to assess the behavior and symptoms associated with ASD. According to research conducted between 2009 and 2017, approximately 17% of children aged three to seventeen have been diagnosed with a developmental impairment such as autism or attention deficit disorder (24) .

Because of changes in diagnostic criteria, the results of European studies have fluctuated throughout time. Studies on this topic from the Middle East are notably scarce. Hussein et al. (2011) discovered that publications on child psychiatry, particularly on topics such as autism, were under-represented in the Arab world (25) According to Hussein and Taha (2013), ASD is not yet a priority in Arab countries, neither in terms of research nor of services. This could be due to the fact that child psychiatry is still relatively new in these cultures (26).

Material and methods:

To conduct this research, relevant articles were looked for in the scientific databases Scopus, Google Scholar, PubMed, and Web of Science using keywords like "Autism, vitamin D, immunoregulatory, Kanner's syndrome, Autistic disease, cytokines."

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Etiology of Autism Spectrum Disorder:

The etiology of ASD has been a topic of discussion for many years . But it's still unclear what causes autism (27, 28). According to studies, genetic and/or environmental factors may contribute to ASD development (29, 30, 31).

Genetic Factor

Autistic spectrum disorder is considered a complex genetic disorder with high inheritance. ASD has a high genetic basis, according to epidemiological twin studies. Fraternal twin concordance is less than 10%, while that for identical twins is between 70–90% (32, 33). There is evidence of family clustering in families where one or more members already have an ASD diagnosis. There is an elevated risk of ASD in younger male siblings of family members with an ASD diagnosis (34, 35). First-degree relatives of ASD carriers have also shown a significant increase in the occurrence of ASD (33). Offspring of parents with ASD or those with a history of psychiatric issues have a much increased risk of developing ASD. After chromosomal and rare syndromes co-occurred with autism in the 1980s, it became obvious that genetic factors play a significant role (36).

Selective candidate gene analysis and whole exome sequencing (WES) are the most extensively used methods for identifying ASD susceptibility genes (37). WES has proven to be a useful tool in the detection of rare or novel genetic abnormalities in a wide range of disorders (38). In spite of the fact that genetic variables have an important etiological role in ASD, empirical research has been unable to convincingly identify particular genes that cause ASD. As a result, more research is needed to study genetic differences.

Environmental Factors

Non-genetic risk factors for autism spectrum disorder may include parental age, maternal nutritional and metabolic state, infection during pregnancy, prenatal stress, and exposure to particular chemicals, heavy metals, or medicines. The age of the parents may have contributed to genetic mutations. Increasing paternal age has been demonstrated to raise the likelihood of ASD in children (39). Nonetheless, some research has refuted this hypothesis (40). Trace metal dyshomeostasis has also been demonstrated to influence brain development and is associated with autism (41). Environmental exposure may have a significant impact on brain development and neurological processes, including cell differentiation, synaptogenesis, and axon myelination (42). ASD has been linked to the accumulation of hazardous metals such as mercury and lead, as well as a lack of the necessary metal zinc during pregnancy, according to epidemiological and animal studies (43).

Maternal infection is an additional non-genetic risk factor for ASD. As a result of the relationship between congenital rubella infections and the development of ASD, the role of immune activation and infections has been continuously evaluated (44). Maternal medication use during pregnancy, particularly antidepressant and antiepileptic drugs, has been linked to an increased incidence of ASD (45). Additionally, a lack of vitamin D during the initial stages of the prenatal period may be linked to an increased risk of autism (46).

Vitamin D’s role in Autism Spectrum Disorder:

Due to vitamin D's active role in fetal neurodevelopment, it may influence the progression of neurodevelopmental diseases, including ASD (47). According to Kittana and his colleagues, the considerable reductions in the ASD severity measures give evidence for the significance of vitamin D in lowering the symptoms of disease.

Children with ASD are frequently observed to have vitamin D deficiency and low serotonin levels in the brain (48). Serotonin levels are linked to the regulation of brain activities such as neurogenesis (49). Both experimental tryptophan and serotonin deprivation reveal autistic-like behavioral traits (48). Insufficiency in vitamin D decreases serotonin levels in the brain by inhibiting the synthesis of tryptophan hydroxylase 2 (TPH2), thus affecting the structure and neuronal wiring of the brain. Individuals with ASD may have a serotonin anomaly, which is defined by high serotonin concentrations in peripheral blood cells, potentially owing to increased gut serotonin synthesis, but minor concentrations in the brain (48).

Seyedi et al. (2019) suggest that vitamin D increases TPH2 gene expression (50) and, consequently, serotonin synthesis in the brain, which can positively influence social behavior and emotional social cues.

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Serotonin deficiency in newborn mice was associated with autism-like behaviors (48, 51). Vitamin D is also important in increasing glutathione peroxidase 1 (GP1) levels, hence lowering oxidative stress (47, 52). Glutathione redox imbalance promotes ASD because it enhances the expression of pro-inflammatory cytokines and has a substantial effect on neuroinflammation (53). Vitamin D is also found to enhance the seizure threshold, thus aiding in the prevention and management of seizures in children (54, 55, 56). According to a study by Malik et al. (2011), increased vitamin D levels may alleviate the symptoms of established autism (57). Due to the fact that activated vitamin D up-regulates DNA-repair genes, vitamin D deficiency during development may impede the repair of DNA mutations in fetuses and newborns, hence increasing the risk of autism. Vitamin D's anti-inflammatory properties may also lessen the likelihood or severity of autism (55, 58).

According to Guillot and colleagues, vitamin D acts as an immunomodulator that decreases inflammation while increasing protective immune responses (59). Direct and indirect anti-inflammatory actions involving both the innate and adaptive immune systems have been observed in animal studies. Vitamin D controls several immune cells, including monocytes, macrophages, dendritic cells, T lymphocytes, and B lymphocytes (60). T-regulatory cells inhibit the responses of other immune cells so that the body does not attack its own tissues. These regulatory T cells, also known as suppressor T cells, are a subpopulation of T cells that suppress the immune system, preserve self-tolerance, and are linked to a lower risk of autoimmune disorders (61). This immunomodulatory impact of vitamin D mediated by T cells may account for the link between vitamin D deficiency and autoimmune disorders (62). Some authors believe that vitamin D may effectively treat certain autoimmune diseases by influencing Tregs and thereby increasing the body's self-tolerance (63,64).

Vitamin D is a fat-soluble vitamin that promotes bone growth and mineralization by facilitating calcium absorption. It also regulates cell differentiation, cell maturation, and the innate immune system as an autocrine and paracrine agent (65, 66). Vitamin D is a group of secosteroids, which are steroid molecules with broken links in steroid rings (67, 68). Vitamin D was first identified as an antirachitic agent between 1919 and 1924. (69). It enters the circulation of the human body through the diet or is generated in the skin from sunlight (68). Vitamin D comes in two primary forms, known collectively as calciferol: Vitamin D2 (ergocalciferol) and Vitamin D3 (cholecalciferol). The presence of a double bond between C22 and C23, as well as a methyl group on C24 on its side chain, distinguishes vitamin D2 from vitamin D3 (70). Most people wrongly believe that vitamin D is similar to other vitamins, i.e., that appropriate levels may be obtained by eating a healthy diet (68). Oily fish like salmon, mackerel, and sardines, as well as fortified foods like cow milk, soy milk, and orange juice, are the primary sources of vitamin D in the usual human diet (70). There was a trend toward significantly better outcomes regarding ASD severity as measured by vitamin D supplementation. This shows that vitamin D may be important, especially in places where the population doesn't get enough of it (47).

Immunology of Autism Spectrum Disorder:

There are two types of immunity: adaptive immunity and innate immunity. According to growing evidence, the immune system plays a significant role in the development of ASD (71). B and T cells, for example, are adaptive immune cells that may induce antigen-specific responses and create immunological memory in the Central Nervous System (CNS) (72). Increased lymphocytes and immunological dysregulation in autistic people's brains may cause astrocyte destruction, compromising the CSF-brain barrier and leading to the development of ASD (73). Microglia-induced abnormal synaptic pruning which impair synaptic plasticity and abnormal series of inflammatory processes including cytokines all contribute to autism (74,75). Evidence of a pathophysiological connection between the immune system and ASD was first described more than 40 years ago (76,77). There are several possible connections and related processes according to subsequent studies on the complex relationship between the immune system and ASD symptoms (78, 79).

Immune Response Abnormalities in Autism Disorder:
Innate Immune Response

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One of the most significant advances in ASD research in the last ten years has been evidence that active neuroinflammation, including chronically activated microglia, is a substantial component of ASD (80). Microglia infiltrate the brain during the earliest stage of embryo and serve critical functions in neurodevelopment, including angiogenesis, synaptic pruning and astrocytic differentiation from neuronal precursor cells (81,82,83,84). The presence of proinflammatory chemokines like MCP-1 in CSF fluid, which is produced by activated microglia, has also been associated with microglia activation in autistic individuals (85). Furthermore, some postmortem investigations have revealed that the structural and morphological properties of microglia in the brains of people with ASD are aberrant (86). Abnormal innate immune responses in ASD patients are not restricted to the brain and CNS; alterations in circulating monocytes, dendritic cells, and NK cells have also been discovered (figure 1). (87). Natural killer cells are essential in the early response of the innate immune system. They specifically attack virally infected cells and play crucial role in tumor monitoring and fetal protection during pregnancy, they can set off a chain reaction of immunological responses as early responders (88). There is a significant amount of evidence that points to the role of NK cells in autism that has a genetic foundation (89). It was shown that people with autism did not have a decrease in their total NK count, which was also found to be the case in patients with schizophrenia (79, 90), implying that the cells themselves are dysfunctional. Warren et al. (1987) discovered decreased NK cell cytotoxicity in autistic patients (91). This deficit in NK cell function has also been seen in autistic people by Enstrom (92). Progenitor cells called monocytes circulate in the blood and differentiate into macrophages upon leaving the blood and entering other body tissues. When triggered by IFN-γ, monocytes and macrophages create more neopterin. Neopterin levels beyond a certain threshold indicate monocyte/macrophage activation and a pro-inflammatory immunological state. Increased monocyte and neopterin levels were seen in autistic children when compared to gender and age-matched healthy controls, indicating that the immune system in ASD children is over-activated (93). Monocytes and macrophages have a wide range of immunomodulatory, inflammatory, and tissue-repairing properties, and they play an active role in the development of many autoimmune disorders (94). These cells have the ability to secrete a variety of cytokines and chemokines that stimulate and recruit extra immune cells to diseased tissue (95,96).

Adaptive Immune Response

The primary components of the adaptive immune system are soluble antibodies and cytokines. Antibodies are glycoproteins generated by memory B cells, which are called plasma cells. Both T cells and B cells, which make up the second arm of the adaptive immune system, have been observed to be changed in autistic individuals. As early as 1986, lower T lymphocyte counts and an altered ratio of helper T cells to suppressor T cells were found (97). Additionally, the presence of many autoantibodies in autism offers indirect evidence that B cells play a role in autism (98).

Plasma IgG and IgM levels were shown to be lower in early children with autism, according to a research that was conducted by Heuer et al. (2008) and included more than 250 children (99). Although there seems to be some inconsistency in studies that reveal increased or reduced IgG levels in children with autism, the age of the children is most likely a contributing factor, as IgG levels are known to change dramatically and fast over the first decade of life (99, 100,101)

Atypical cellular immunity may be indicated by changes in cytokine concentrations or production. The levels of Th2 and Th1 T-cell cytokines were considerably greater in the autistic group in a research comparing their production in peripheral blood mononuclear cells (102). Some pro-inflammatory cytokines, such as Th1 cytokines, have been linked to the severity of clinical behavioral outcomes, such as aberrant behaviors and poor communication, in children with ASD (103).

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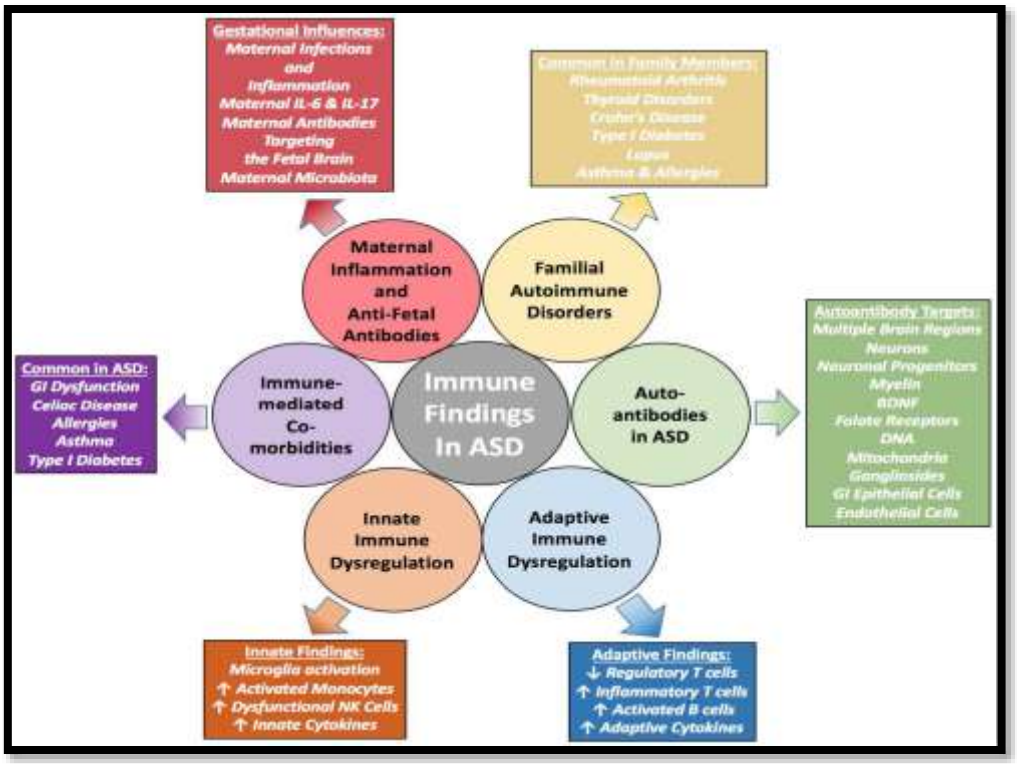

Figure 1: .Innate/Adaptive Immune dysregulation (Hughes et al., 2018)

Role of Cytokines in Autism Spectrum Disorder:

Although it is widely accepted that cytokine mediators are components of the disturbed immunological milieu found in autism, there is significant disagreement over how such changes manifest, especially whether the pro-inflammatory or anti-inflammatory cellular response predominates. Several researches have proven a relationship between levels of cytokines and autistic behavior development (104,105). This is attributable to pro-inflammatory and anti-inflammatory cytokines' ability to interact with immune cells as well as neuroendocrine system messengers, which primarily includes neurotransmitters and hormones (106). These cytokines have been demonstrated to interfere with the activity of serotonin transporters as well as the diurnal secretion of hypothalamic–pituitary–adrenal (HPA) axis hormones (107,108). As a result, it is not surprising that, over the last decade, cytokine levels have been increasingly related to various neuropsychiatric disorders, most notably depression, schizophrenia, and autism (106,109,110,111). The activation of astroglia and microglia cells, as well as elevated proinflammatory cytokine levels throughout life, implies a neuroinflammatory phenotype in ASD, which may play a crucial role in the development of ASD behavior (112). ASD has been linked to a number of inflammatory cytokines and immunological markers that indicate immune dysfunction (113).

Vitamin D's therapeutic effects on cytokine modulation and autism spectrum disorder

Pro-inflammatory cytokines such IL-6, and IFN-γ were reported to be more abundant in children with ASD. Increases in these levels are connected to cognitive impairment in autism (114). It is believed that vitamin D metabolites promote the production of anti-inflammatory cytokines and produce a more tolerogenic state in dendritic cells (115). Anti-inflammatory cytokines decrease the action of pro-inflammatory cytokines, which is seen in autism. Vitamin D preserves brain tissue by decreasing the synthesis of inflammatory cytokines (116).

Numerous studies have demonstrated that taking vitamin D supplements helps by improving ASD symptoms. A 3-year-old child who took 400 IU of vitamin D daily for two months shows a significant improvement in the main symptoms of ASD as well as a study conducted by Azzam revealed that ASD children's Intelligence quotient were better after 3 month of vitamin D treatment (117,118). A recent clinical trial indicated that daily high-dose of vitamin D (300 U/kg/d) supplementation improved ASD children's CARS score, stereotypes, eye contact, and attention (119,120).

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Conclusion:
The increased prevalence of ASD has made it a social concern requiring immediate solutions, yet its source remains unknown. The focus of researchers on the discovery of relevant biological measurements is largely due to the ASD's distinctive heterogeneity. It is vital to examine the etiology and pathophysiology of ASD from a different angle in order to generate novel treatment strategies for ASD. Previously studied cytokine abnormalities in ASD have drawn attention to a potential connection between immune dysregulation and ASD. Because vitamin D plays an active role in fetal neurodevelopment, low vitamin D levels in gestation, postnatal, and in early infancy have been proposed as a risk factor for neurodevelopmental disorders, including ASD. The findings from the reviewed experimental investigations support the importance of vitamin D in lowering ASD as well as indicate substantial reductions in ASD severity measures by modulating and affecting the immune system and cytokines. Alterations in cytokine levels could make it easier to diagnose ASD and might offer biological markers that make it easier to track the success of active therapies during clinical trials, which can help us find more specific treatments for autism-related symptoms. If future research makes the link between vitamin D and ASD clearer, a simple, cheap, and safe new way to prevent and treat ASD would become available.

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References:
1-Lord C, Charman T, Cusack J, Guillaume D, Frazier T, Jones RM, Pickles A, Lounds TJ, Jeremy VV. Autism spectrum disorder (primer). Nature Reviews: Disease Primers. 2020;6(1).
2-Zhao H, Zhang H, Liu S, Luo W, Jiang Y, Gao J. Association of peripheral blood levels of cytokines with autism spectrum disorder: A meta-analysis. Frontiers in psychiatry. 2021 Jul 2;12:1006.
3-Tawhid MN, Siuly S, Wang H. Diagnosis of autism spectrum disorder from EEG using a time–frequency spectrogram image-based approach. Electronics Letters. 2020 Dec;56(25):1372-5.
4-Lazoff T, Zhong L, Piperni T, Fombonne E. Prevalence of pervasive developmental disorders among children at the English Montreal School Board. The Canadian Journal of Psychiatry. 2010 Nov;55(11):715-20.
5-Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, Kurzius-Spencer M, Zahorodny W, Rosenberg CR, White T, Durkin MS. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveillance Summaries. 2018 Apr 27;67(6):1.
6-Noriega G. Restricted, repetitive, and stereotypical patterns of behavior in autism—an fmri perspective. IEEE Transactions on Neural Systems and Rehabilitation Engineering. 2019 Apr 22;27(6):1139-48.
7-Hong MP, Erickson CA. Investigational drugs in early-stage clinical trials for autism spectrum disorder. Expert Opinion on Investigational Drugs. 2019 Aug 3;28(8):709-18.
8-Krebs NF, Lozoff B, Georgieff MK. Neurodevelopment: the impact of nutrition and inflammation during infancy in low-resource settings. Pediatrics. 2017 Apr;139(Supplement_1):S50-8.
9-Lee BK, Eyles DW, Magnusson C, Newschaffer CJ, McGrath JJ, Kvaskoff D, Ko P, Dalman C, Karlsson H, Gardner RM. Developmental vitamin D and autism spectrum disorders: findings from the Stockholm Youth Cohort. Molecular psychiatry. 2021 May;26(5):1578-88.
10-Anjos T, Altmäe S, Emmett P, Tiemeier H, Closa-Monasterolo R, Luque V, Wiseman S, Pérez-García M, Lattka E, Demmelmair H, Egan B. Nutrition and neurodevelopment in children: focus on NUTRIMENTHE project. European journal of nutrition. 2013 Dec;52(8):1825-42.
11-Schwarzenberg SJ, Georgieff MK, Daniels S, Corkins M, Golden NH, Kim JH, Lindsey C, Magge SN. Advocacy for improving nutrition in the first 1000 days to support childhood development and adult health. Pediatrics. 2018 Feb 1;141(2).
12-Cannell JJ. Vitamin D and autism, what's new?. Reviews in Endocrine and Metabolic Disorders. 2017 Jun;18(2):183-93.

ISSN NO: 2770-2936
Date of Publication:04-08-2022

13-Gil Á, Plaza-Diaz J, Mesa MD. Vitamin D: classic and novel actions. Annals of Nutrition and Metabolism. 2018;72(2):87-95.
14-Siracusano M, Riccioni A, Abate R, Benvenuto A, Curatolo P, Mazzone L. Vitamin D deficiency and autism spectrum disorder. Current Pharmaceutical Design. 2020 Jun 1;26(21):2460-74.
15- Şengenç E, Kıykım E, Saltik S. Vitamin D levels in children and adolescents with autism. Journal of International Medical Research. 2020 Jul;48(7):0300060520934638.
16-Liu W, Zhang L, Xu HJ, Li Y, Hu CM, Yang JY, Sun MY. The anti-inflammatory effects of vitamin D in tumorigenesis. International journal of molecular sciences. 2018 Sep 13;19(9):2736.
17-Masi A, Quintana DS, Glozier N, Lloyd AR, Hickie IB, Guastella AJ. Cytokine aberrations in autism spectrum disorder: a systematic review and meta-analysis. Molecular psychiatry. 2015 Apr;20(4):440-6.
18-Evans B. How autism became autism: The radical transformation of a central concept of child development in Britain. History of the human sciences. 2013 Jul;26(3):3-1.
19-Feinstein A. A history of autism: Conversations with the pioneers. John Wiley & Sons; 2011 Jul 7.
20-Atkins Jr WE. *The history and significance of the autism spectrum* (Doctoral dissertation, University of Toledo).
21-Kim SH, Lord C. Restricted and repetitive behaviors in toddlers and preschoolers with autism spectrum disorders based on the Autism Diagnostic Observation Schedule (ADOS). Autism Research. 2010 Aug;3(4):162-73.
22-Fombonne E, MacFarlane H, Salem AC. Epidemiological surveys of ASD: advances and remaining challenges. Journal of autism and developmental disorders. 2021 Dec;51(12):4271-90.
23-Christensen DL, Braun KV, Baio J, Bilder D, Charles J, Constantino JN, Daniels J, Durkin MS, Fitzgerald RT, Kurzius-Spencer M, Lee LC. Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2012. MMWR Surveillance Summaries. 2018 Nov 11;65(13):1.
24-Maenner MJ, Shaw KA, Baio J, Washington A, Patrick M, DiRienzo M, Christensen DL, Wiggins LD, Pettygrove S, Andrews JG, Lopez M. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2016. MMWR Surveillance summaries. 2020 Mar 3;69(4):1.
25-Hussein H, Taha GR, Almanasef A. Characteristics of autism spectrum disorders in a sample of egyptian and saudi patients: transcultural cross sectional study. Child and adolescent psychiatry and mental health. 2011 Dec;5(1):1-2.
26-Hussein H, Taha GR. Autism spectrum disorders: a review of the literature from Arab countries. Middle East Current Psychiatry. 2013 Jul 1;20(3):106-16.
27-Russell G, Kelly S, Golding J. A qualitative analysis of lay beliefs about the aetiology and prevalence of autistic spectrum disorders. Child: care, health and development. 2010 May;36(3):431-6.
28-Yousef AM, Roshdy EH, Fattah NR, Said RM, Atia MM, Hafez EM, Mohamed AE. Prevalence and risk factors of autism spectrum disorders in preschool children in Sharkia, Egypt: A community-based study. Middle East Current Psychiatry. 2021 Dec;28(1):1-4.
29-Newschaffer CJ, Croen LA, Daniels J, Giarelli E, Grether JK, Levy SE, Mandell DS, Miller LA, Pinto-Martin J, Reaven J, Reynolds AM. The epidemiology of autism spectrum disorders. Annual review of public health. 2007 Apr 21;28:235.
30-Landrigan PJ, Lambertini L, Birnbaum LS. A research strategy to discover the environmental causes of autism and neurodevelopmental disabilities. Environmental health perspectives. 2012 Jul;120(7):a258-60.
31-AlSagob M, Colak D, Kaya N. Genetics of autism spectrum disorder: an update on copy number variations leading to autism in the next generation sequencing era. Discovery medicine. 2015 May 27;19(106):367-79.
32-Sauer AK, Stanton J, Hans S, Grabrucker A. Autism Spectrum disorders: Etiology and pathology. Exon Publications. 2021 Aug 20:1-5.
33-Abrahams BS, Geschwind DH. Advances in autism genetics: on the threshold of a new neurobiology. Nature reviews genetics. 2008 May;9(5):341-55.

ISSN NO: 2770-2936
Date of Publication:04-08-2022

34 -Genovese A, Butler MG. Clinical assessment, genetics, and treatment approaches in autism spectrum disorder (ASD). International journal of molecular sciences. 2020 Jul 2;21(13):4726. https://doi.org/10.3390/ijms21134726

35-Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L. & Stone, WL. Recurrence risk for autism spectrum disorders: A baby siblings research consortium study. Pediatrics.2011 ;128:e1-8.

36-Blomquist HK, Bohman M, Edvinsson SO, Gillberg C, Gustavson KH, Holmgren G, Wahlström J. Frequency of the fragile X syndrome in infantile autism. Clinical genetics. 1985 Feb;27(2):113-7.

37-Persico AM, Napolioni V. Autism genetics. Behavioural brain research. 2013 Aug 15;251:95-112.

38-Rabbani B, Tekin M, Mahdieh N. The promise of whole-exome sequencing in medical genetics. Journal of human genetics. 2014 Jan;59(1):5-15.

39- Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Advanced parental age and autism risk in children: a systematic review and meta-analysis. Acta Psychiatrica Scandinavica. 2017 Jan;135(1):29-41.. *https://doi.org/10.1111/ acps.12666*

40-Karimi P, Kamali E, Mousavi SM, Karahmadi M. Environmental factors influencing the risk of autism. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2017;22.

41-Hagmeyer S, Mangus K, Boeckers TM, Grabrucker AM. Effects of trace metal profiles characteristic for autism on synapses in cultured neurons. Neural Plasticity. 2015 Oct;2015.

42-Lyall K, Schmidt RJ, Hertz-Picciotto I. Maternal lifestyle and environmental risk factors for autism spectrum disorders. International journal of epidemiology. 2014 Apr 1;43(2):443-64.

43-Rossignol DA, Genuis SJ, Frye RE. Environmental toxicants and autism spectrum disorders: a systematic review. Translational psychiatry. 2014 Feb;4(2):e360-.

44-Careaga M, Murai T, Bauman MD. Maternal immune activation and autism spectrum disorder: from rodents to nonhuman and human primates. Biological psychiatry. 2017 Mar 1;81(5):391-401.

45- Emberti Gialloreti L, Mazzone L, Benvenuto A, Fasano A, Garcia Alcon A, Kraneveld A, Moavero R, Raz R, Riccio MP, Siracusano M, Zachor DA. Risk and protective environmental factors associated with autism spectrum disorder: evidence-based principles and recommendations. Journal of clinical medicine. 2019 Feb 8;8(2):217. *https://doi.org/10.3390/jcm8020217*

46-Vinkhuyzen AA, Eyles DW, Burne TH, Blanken LM, Kruithof CJ, Verhulst F, White T, Jaddoe VW, Tiemeier H, McGrath JJ. Gestational vitamin D deficiency and autism spectrum disorder. BJPsych open. 2017 Mar;3(2):85-90.

47-Kittana M, Ahmadani A, Stojanovska L, Attlee A. The Role of Vitamin D Supplementation in Children with Autism Spectrum Disorder: A Narrative Review. Nutrients. 2021 Dec 22;14(1):26.

48-Patrick RP, Ames BN. Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. The FASEB Journal. 2014 Jun;28(6):2398-413.

49-Berridge MJ. Vitamin D deficiency: infertility and neurodevelopmental diseases (attention deficit hyperactivity disorder, autism, and schizophrenia). American Journal of Physiology-Cell Physiology. 2018 Feb 1;314(2):C135-51.

50-Seyedi M, Gholami F, Samadi M, Djalali M, Effatpanah M, Yekaninejad MS, Hashemi R, Abdolahi M, Chamari M, Honarvar NM. The effect of vitamin D3 supplementation on serum BDNF, dopamine, and serotonin in children with attention-deficit/hyperactivity disorder. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2019 Aug 1;18(6):496-501.

51-Sabir MS, Haussler MR, Mallick S, Kaneko I, Lucas DA, Haussler CA, Whitfield GK, Jurutka PW. Optimal vitamin D spurs serotonin: 1, 25-dihydroxyvitamin D represses serotonin reuptake transport (SERT) and degradation (MAO-A) gene expression in cultured rat serotonergic neuronal cell lines. Genes & nutrition. 2018 Dec;13(1):1-1.

52-Ansari MG, Sabico S, Clerici M, Khattak MN, Wani K, Al-Musharaf S, Amer OE, Alokail MS, Al-Daghri NM. Vitamin D supplementation is associated with increased glutathione peroxidase-1 levels in Arab adults with prediabetes. Antioxidants. 2020 Jan 29;9(2):118.

53-Bjørklund G, Tinkov AA, Hosnedlová B, Kizek R, Ajsuvakova OP, Chirumbolo S, Skalnaya MG, Peana M, Dadar M, El-Ansary A, Qasem H. The role of glutathione redox imbalance in autism spectrum disorder: a review. Free Radical Biology and Medicine. 2020 Nov 20;160:149-62.

ISSN NO: 2770-2936
Date of Publication:04-08-2022

54-Kočovská E, Fernell E, Billstedt E, Minnis H, Gillberg C. Vitamin D and autism: clinical review. Research in developmental disabilities. 2012 Sep 1;33(5):1541-50.
55-Cannell JJ, Grant WB. What is the role of vitamin D in autism?. Dermato-endocrinology. 2013 Jan 1;5(1):199-204.
56-Frye RE, Casanova MF, Fatemi SH, Folsom TD, Reutiman TJ, Brown GL, Edelson SM, Slattery JC, Adams JB. Neuropathological mechanisms of seizures in autism spectrum disorder. Frontiers in neuroscience. 2016 May 10;10:192.
57-Malik M, Sheikh AM, Wen G, Spivack W, Brown WT, Li X. Expression of inflammatory cytokines, Bcl2 and cathepsin D are altered in lymphoblasts of autistic subjects. Immunobiology. 2011 Jan 1;216(1-2):80-5.
58-Saad K, Abdel-Rahman AA, Elserogy YM, Al-Atram AA, Cannell JJ, Bjørklund G, Abdel-Reheim MK, Othman HA, El-Houfey AA, Abd El-Aziz NH, Abd El-Baseer KA. Vitamin D status in autism spectrum disorders and the efficacy of vitamin D supplementation in autistic children. Nutritional neuroscience. 2016 Sep 13;19(8):346-51.
59-Guillot X, Semerano L, Saidenberg-Kermanac'h N, Falgarone G, Boissier MC. Vitamin D and inflammation. Joint Bone Spine. 2010 Dec 1;77(6):552-7.
60-Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. Current opinion in pharmacology. 2010 Aug 1;10(4):482-96. http://dx.doi.org/10.1016/j.coph.2010.04.001
61-Dimeloe S, Nanzer A, Ryanna K, Hawrylowicz C. Regulatory T cells, inflammation and the allergic response—the role of glucocorticoids and vitamin D. The Journal of steroid biochemistry and molecular biology. 2010 May 31;120(2-3):86-95. http://dx.doi.org/10.1016/j. jsbmb.2010.02.029
62-Toubi E, Shoenfeld Y. The role of vitamin D in regulating immune responses. The Israel Medical Association journal: IMAJ. 2010 Mar;12(3):174-5.
63- Pedersen AW, Claesson MH, Zocca MB. Dendritic cells modified by vitamin D: future immunotherapy for autoimmune diseases. Vitamins & Hormones. 2011 Jan 1;86:63-82. http://dx.doi.org/10.1016/B978-0-12-386960-9.00003-4
64-Mostafa GA, Al Shehab A, Fouad NR. Frequency of CD4+ CD25high regulatory T cells in the peripheral blood of Egyptian children with autism. Journal of child neurology. 2010 Mar;25(3):328-35. http:// dx.doi.org/10.1177/0883073809339393
65-Nair R, Maseeh A. Vitamin D: The "sunshine" vitamin. Journal of Pharmacology and Pharmacotherapeutics. 2012 Jun;3(2):118-26.
66-Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chemistry & biology. 2014 Mar 20;21(3):319-29.
67-Di Rosa M, Malaguarnera M, Nicoletti F, Malaguarnera L. Vitamin D3: a helpful immuno-modulator. Immunology. 2011 Oct;134(2):123-39.
68-White JH. Vitamin D metabolism and signaling in the immune system. Reviews in endocrine and metabolic disorders. 2012 Mar;13(1):21-9.
69-Wolf G. The discovery of vitamin D: the contribution of Adolf Windaus. The Journal of nutrition. 2004 Jun;134(6):1299-302.
70-Holick MF. Vitamin D: a D-Lightful health perspective. Nutrition reviews. 2008 Oct 1;66(suppl_2):S182-94.
71-Jones KL, Pride MC, Edmiston E, Yang M, Silverman JL, Crawley JN, Van de Water J. Autism-specific maternal autoantibodies produce behavioral abnormalities in an endogenous antigen-driven mouse model of autism. Molecular psychiatry. 2020 Nov;25(11):2994-3009.
72- Pangrazzi L, Balasco L, Bozzi Y. Oxidative stress and immune system dysfunction in autism spectrum disorders. International journal of molecular sciences. 2020 May 6;21(9):3293. *doi: 10.3390/ijms21093293*
73-DiStasio MM, Nagakura I, Nadler MJ, Anderson MP. T lymphocytes and cytotoxic astrocyte blebs correlate across autism brains. Annals of neurology. 2019 Dec;86(6):885-98. doi: 10.1002/ana.25610
74-Saitoh BY, Tanaka E, Yamamoto N, van Kruining D, Iinuma K, Nakamuta Y, Yamaguchi H, Yamasaki R, Matsumoto K, Kira JI. Early postnatal allergic airway inflammation induces dystrophic microglia leading to excitatory postsynaptic surplus and autism-like behavior. Brain, Behavior, and Immunity. 2021 Jul 1;95:362-80. doi: 10.1016/j.bbi.2021.04.008

ISSN NO: 2770-2936
Date of Publication:04-08-2022

75-Matta SM, Hill-Yardin EL, Crack PJ. The influence of neuroinflammation in Autism Spectrum Disorder. Brain, behavior, and immunity. 2019 Jul 1;79:75-90.doi: 10.1016/j.bbi.2019.04.037
76-Stubbs E, Crawford ML, Burger DR, Vandenbark AA. Depressed lymphocyte responsiveness in autistic children. Journal of autism and childhood schizophrenia. 1977 Mar;7(1):49-55.
77-Onore C, Careaga M, Ashwood P. The role of immune dysfunction in the pathophysiology of autism. Brain, behavior, and immunity. 2012 Mar 1;26(3):383-92. https://doi.org/10.1016/j.bbi.2011.08.007
78-Goines P, Van de Water J. The immune system's role in the biology of autism. Current opinion in neurology. 2010 Apr;23(2):111.
79-Meltzer A, Van de Water J. The role of the immune system in autism spectrum disorder. Neuropsychopharmacology. 2017 Jan;42(1):284-98.
80-Prata J, Santos SG, Almeida MI, Coelho R, Barbosa MA. Bridging Autism Spectrum Disorders and Schizophrenia through inflammation and biomarkers-pre-clinical and clinical investigations. Journal of neuroinflammation. 2017 Dec;14(1):1-33.
81- Rymo SF, Gerhardt H, Wolfhagen Sand F, Lang R, Uv A, Betsholtz C. A two-way communication between microglial cells and angiogenic sprouts regulates angiogenesis in aortic ring cultures. PloS one. 2011 Jan 10;6(1):e15846. doi: 10.1371/journal.pone.0015846
82- Nakanishi M, Niidome T, Matsuda S, Akaike A, Kihara T, Sugimoto H. Microglia-derived interleukin-6 and leukaemia inhibitory factor promote astrocytic differentiation of neural stem/progenitor cells. European Journal of Neuroscience. 2007 Feb;25(3):649-58. doi: 10.1111/j.1460-9568.2007.05309.x
83-Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, Giustetto M, Ferreira TA, Guiducci E, Dumas L, Ragozzino D. Synaptic pruning by microglia is necessary for normal brain development. science. 2011 Sep 9;333(6048):1456-8. doi: 10.1126/science.1202529
84-Sierra A, Encinas JM, Deudero JJ, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, Tsirka SE, Maletic-Savatic M. Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. Cell stem cell. 2010 Oct 8;7(4):483-95. doi: 10.1016/j.stem.2010.08.014
85-Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2005 Jan;57(1):67-81.
86-Koyama R, Ikegaya Y. Microglia in the pathogenesis of autism spectrum disorders. Neuroscience research. 2015 Nov 1;100:1-5.
87-Hughes HK, Mills Ko E, Rose D, Ashwood P. Immune dysfunction and autoimmunity as pathological mechanisms in autism spectrum disorders. Frontiers in cellular neuroscience. 2018 Nov 13;12:405.
88- Mandal A, Viswanathan C. Natural killer cells: In health and disease. Hematology/oncology and stem cell therapy. 2015 Jun 1;8(2):47-55. doi: 10.1016/j.hemonc.2014.11.006
89-Lintas C, Sacco R, Persico AM. Genome-wide expression studies in autism spectrum disorder, Rett syndrome, and Down syndrome. Neurobiology of disease. 2012 Jan 1;45(1):57-68.
90-DeLisi LE, Ortaldo JR, Maluish AE, Wyatt RJ. Deficient natural killer cell (NK) activity and macrophage functioning in schizophrenic patients. Journal of neural transmission. 1983 Mar;58(1):99-106.
91-Warren RP, Foster AN, Margaretten NC. Reduced natural killer cell activity in autism. Journal of the American Academy of Child & Adolescent Psychiatry. 1987 May 1;26(3):333-5.
92-Enstrom AM, Lit L, Onore CE, Gregg JP, Hansen RL, Pessah IN, Hertz-Picciotto I, Van de Water JA, Sharp FR, Ashwood P. Altered gene expression and function of peripheral blood natural killer cells in children with autism. Brain, behavior, and immunity. 2009 Jan 1;23(1):124-33.
93-Sweeten TL, Posey DJ, McDougle CJ. High blood monocyte counts and neopterin levels in children with autistic disorder. American Journal of Psychiatry. 2003 Sep 1;160(9):1691-3.
94-Laria A, Lurati A, Marrazza M, Mazzocchi D, Re KA, Scarpellini M. The macrophages in rheumatic diseases. Journal of inflammation research. 2016;9:1. doi: 10.2147/JIR.S82320
95- Navegantes KC, de Souza Gomes R, Pereira PA, Czaikoski PG, Azevedo CH, Monteiro MC. Immune modulation of some autoimmune diseases: the critical role of macrophages and neutrophils in the innate and adaptive immunity. Journal of translational medicine. 2017 Dec;15(1):1-21. doi: 10.1186/s12967-017-1141-8

ISSN NO: 2770-2936
Date of Publication:04-08-2022

96-Ma WT, Chang C, Gershwin ME, Lian ZX. Development of autoantibodies precedes clinical manifestations of autoimmune diseases: a comprehensive review. Journal of autoimmunity. 2017 Sep 1;83:95-112. doi: 10.1016/j.jaut.2017.07.003
97-Warren RP, Margaretten NC, Pace NC, Foster A. Immune abnormalities in patients with autism. Journal of autism and developmental disorders. 1986 Jun;16(2):189-97.
98-Careaga M, Ashwood P. Autism spectrum disorders: from immunity to behavior. InPsychoneuroimmunology 2012 (pp. 219-240). Humana Press, Totowa, NJ.
99-Heuer L, Ashwood P, Schauer J, Goines P, Krakowiak P, Hertz-Picciotto I, Hansen R, Croen LA, Pessah IN, Van de Water J. Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms. Autism Research. 2008 Oct;1(5):275-83.
100-Enstrom A, Krakowiak P, Onore C, Pessah IN, Hertz-Picciotto I, Hansen RL, Van de Water JA, Ashwood P. Increased IgG4 levels in children with autism disorder. Brain, behavior, and immunity. 2009 Mar 1;23(3):389-95.
101-Zaman S, Yazdani U, Deng Y, Li W, Gadad BS, Hynan L, Karp D, Roatch N, Schutte C, Nathan Marti C, Hewitson L. A search for blood biomarkers for autism: peptoids. Scientific reports. 2016 Jan 14;6(1):1-8.
102-Molloy CA, Morrow AL, Meinzen-Derr J, Dawson G, Bernier R, Dunn M, Hyman SL, McMahon WM, Goudie-Nice J, Hepburn S, Minshew N. Familial autoimmune thyroid disease as a risk factor for regression in children with Autism Spectrum Disorder: a CPEA Study. Journal of autism and developmental disorders. 2006 Apr;36(3):317-24.
103-Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah I, Van de Water J. Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. Brain, behavior, and immunity. 2011 Jan 1;25(1):40-5.
104-Enstrom AM, Onore CE, Van de Water JA, Ashwood P. Differential monocyte responses to TLR ligands in children with autism spectrum disorders. Brain, behavior, and immunity. 2010 Jan 1;24(1):64-71.
105-Ricci S, Businaro R, Ippoliti F, Lo Vasco VR, Massoni F, Onofri E, Troili GM, Pontecorvi V, Morelli M, Rapp Ricciardi M, Archer T. Altered cytokine and BDNF levels in autism spectrum disorder. Neurotoxicity research. 2013 Nov;24(4):491-501.
106-Saghazadeh A, Ataeinia B, Keynejad K, Abdolalizadeh A, Hirbod-Mobarakeh A, Rezaei N. Anti-inflammatory cytokines in autism spectrum disorders: A systematic review and meta-analysis. Cytokine. 2019 Nov 1;123:154740.
107-Zhu CB, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. Neuropsychopharmacology. 2006 Oct;31(10):2121-31.
108-Raison CL, Borisov AS, Woolwine BJ, Massung B, Vogt G, Miller AH. Interferon-α effects on diurnal hypothalamic–pituitary–adrenal axis activity: relationship with proinflammatory cytokines and behavior. Molecular psychiatry. 2010 May;15(5):535-47.
109-Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. Biological psychiatry. 2010 Mar 1;67(5):446-57.
110-Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell. 2013 Dec 19;155(7):1451-63.
111-Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biological psychiatry. 2013 Jul 1;74(1):15-25.
112-Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2005 Jan;57(1):67-81.
113-Ratajczak HV. Theoretical aspects of autism: biomarkers—a review. Journal of immunotoxicology. 2011 Mar 1;8(1):80-94.
114- Napolioni V, Ober-Reynolds B, Szelinger S, Corneveaux JJ, Pawlowski T, Ober-Reynolds S, Kirwan J, Persico AM, Melmed RD, Craig DW, Smith CJ. Plasma cytokine profiling in sibling pairs discordant for autism spectrum disorder. Journal of neuroinflammation. 2013 Dec;10(1):1-2. doi: 10.1186/1742-2094-10-38

ISSN NO: 2770-2936
Date of Publication:04-08-2022

115-Krakowiak P, Goines PE, Tancredi DJ, Ashwood P, Hansen RL, Hertz-Picciotto I, Van de Water J. Neonatal cytokine profiles associated with autism spectrum disorder. Biological psychiatry. 2017 Mar 1;81(5):442-51. doi: 10.1016/j.biopsych.2015.08.007

116- Mazahery H, Camargo Jr CA, Conlon C, Beck KL, Kruger MC, Von Hurst PR. Vitamin D and autism spectrum disorder: a literature review. Nutrients. 2016 Apr 21;8(4):236.. doi: 10.3390/nu8040236

117-Jia F, Wang B, Shan L, Xu Z, Staal WG, Du L. Core symptoms of autism improved after vitamin D supplementation. Pediatrics. 2015 Jan;135(1):e196-8. doi: 10.1542/peds.2014-2121

118-Azzam HM, Sayyah H, Youssef S, Lotfy H, Abdelhamid IA, Abd Elhamed HA, Maher S. Autism and vitamin D: An intervention study. Middle East Current Psychiatry. 2015 Jan 1;22(1):9-14. doi: 10.1097/01.Xme.0000457269.05570.78

119-Saad K, Abdel-Rahman AA, Elserogy YM, Al-Atram AA, El-Houfey AA, Othman HA, Bjørklund G, Jia F, Urbina MA, Abo-Elela MG, Ahmad FA. Retracted: Randomized controlled trial of vitamin D supplementation in children with autism spectrum disorder. Journal of Child Psychology and Psychiatry. 2018 Jan;59(1):20-9. doi: 10.1111/jcpp.12652

120-Feng J, Shan L, Du L, Wang B, Li H, Wang W, Wang T, Dong H, Yue X, Xu Z, Staal WG. Clinical improvement following vitamin D3 supplementation in autism spectrum disorder. Nutritional neuroscience. 2017 May 28;20(5):284-90. doi: 10.1080/1028415x.2015.1123847