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Autism and Food Allergy

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Introduction

The prevalence of food allergy is up to 5% in the first year of life, and autism spectrum disorders (ASD) (6.0/1,000) is predominant in early childhood. The prevalence of autism and allergy has risen dramatically in the last two decades causing a major public health issues in the developed countries. One of the main issues discussed in this chapter is that, why despite a few number of foods are involved in food allergy, it`s prevalence is rising worldwide? Neuroimmune system has an essential role in neuroinflammation and behavioral changes in autism. Today, we know that food allergies effect on neural responses. Mast cells are abundant in the deep parts of the central nervous system. Mast cells have numerous granules that during degranulation, release histamine and other mediators which can stimulate the central nervous system. Histamine H3 receptors predominantly exist in the brain. Mast cell interactions with the nerve cells result in neuroinflammation and neurodegeneration which can disrupt the blood-brain barrier (BBB). In addition, food intolerance, food chemical sensitivities, and food poisoning are non-immunological responses to food that have similar symptoms and signs of food allergy. Furthermore, some of the peptide fragments such as gluten and casein (specifically gluteomorphin and casomorphin) can mimic some chemicals in the brain called endorphins.

Despite the fact that food allergy affects approximately 6-8 percent of people, most of the times it is a hidden disorder. So most of the people are unaware of their allergy and do not seek treatment [1,2]. Furthermore, common clinical symptoms of patients with food allergies, other behavioral symptoms including sleep, social interaction and, learning disorders, irritability, stress, anxiety, and depression may be observed in the children suffering from Child food allergy [3]. The key question is that do autistic children with food allergy, talk to their parents or teachers about their problems? Even in normal children with food allergies, many of these symptoms are hidden. This chapter focuses on the relationship between autism and child food allergies. To get started it is important to define the following terms:

1) Autism refers to disorder with neurodevelopmental etiology which is characterized by behavioral, social and communication impairments. 2) Child food allergy refers to a growing phenomenon especially in developed countries with a prevalence of 6% to 10% of the pediatric population. 3) Neuroinflammation refers to immune responses in the CNS in response to a wide variety of stimuli. Nowadays, one of the common concerns of immunologists and neurologists is the neuroinflammation issue in various neurodegenerative diseases. The inflammatory response that occurs in the brain is called neuroinflammation [4]. Microglial cells and astrocytes are the main cells that respond to the released mediators of the anti- inflammatory cells and are getting hurt or injured. Brain mast cells are an important source for producing anti-inflammatory molecules. They interact with the neurons and microglial cells, which leads to the release of various mediators, cytokines, proteases and oxygen-derived free radicals inside the brain tissue. The increased level of these mediators during the inflammation has negative effects on the neurogenesis, neurodegeneration, and permeability of the BBB inside the brain tissue. Furthermore, the amount of mitochondrial extra-cellular compounds and anti-inflammatory cytokines including IL-6, TNF-α and GM-CSF and chemoattractants such as MCP-1 are significantly higher inside the brain tissue of patients suffering from autism.

Gastrointestinal track also plays an important role in the immune responses, because it contains a large number of immune cells, mucosal immune tissue, and micro-organisms, which affects the brain. The gastrointestinal symptoms such as abdominal pain, diarrhea, and constipation are often observed in children with autism. Initially, these symptoms are likely to be a sign of an allergic reaction or are increased upon allergic reaction in this disease. The microbial imbalance can also be a major factor in neuronal disorders. Recent investigations have shown that there is a relation between similar autistic behavior and the gastrointestinal phenotypes with changed microbiota. Understanding the early interactions between the intestinal microbiota and autism are essential for the effective nutritional interventions in high-risk populations.

Mast cells are the first responder cells inside the brain, which can initiate and develop the immune responses in the nervous tissues. They respond to the various chemical stimuli, such as allergens, antigens, complement, drugs, and traumas and are contributed using the degranulation of their toxic granules in the inflammatory reactions. Today, there is a strong possibility that these cells contribute to the incidence of brain disorders such as MS, Alzheimer's, and Autism [5-7].

The presence of neurotensin, which is a neuropeptide inside the brain, contributes to the trigger severe inflammatory reactions inside an autistic brain. The brain mast cells are known as "immune gate to brain" cells. They are abundantly seen in the hypothalamus. The brain mast cells in CNS are closely interconnected with the neurons, which is an important part of the beginning of a neuroinflammation process inside the brain. Mast cells' function in the induction of neuroinflammation, which is one of the most promoting factors in autistic patients, will be evaluated in this chapter. As an example, mast cells can change the susceptibility of the neurons using the heparin transgranulation [4].

Inflammation is an innate immune system response that has a protecting role and usually leads to elimination of the destructive agent. BBB existence is considered a crucial advantage in the CNS. Due to the unique feature of the CNS, neuroinflammation is distinguished from the inflammation inside other tissues. Generally, inflammation is primarily a way of protecting tissues that have its benefits but stable neuroinflammation causes tissue injuries by effecting on the brain parenchyma and BBB structure, which can lead to neuronal death. To

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find out how to form an inflammation associated with mast cells inside the brain, the discussions will be addressed in the following chapter [4].

The role of the cytokines in autism has long been in the center of attention and evaluation for researchers. Undoubtedly, it is known as one of the promotive factors of this disease now. During the early stages of assessment, anti-inflammatory cytokines may have stable harmful effects on the brain. Therefore, the following prenatal exposures to anti-inflammatory cytokines damage the hippocampus and spatial memory. Besides, loss of nerves and nerve damage in veins has been observed. Therefore, the inflammatory cytokines and cytokines, which cause neuroinflammation, are involved in both the inflammatory responses and neuroprotective processes. During the constant stress conditions, the anti-inflammatory cytokines have been released, which lead to chronic neuroinflammation that is a promotive factor associated with autism [8-11].

Clinical Manifestations of Food Allergic Disease

According to the clinical findings and Coombs and Gell classification, the food allergies are hypersensitivity diseases, which are dependent on the immunoglobulin E (IgE) that is a classical Type I hypersensitivity mechanism. IgE plays an important role in the pathophysiology of food allergy and other allergic diseases. In children cases, IgE levels in serum increase continuously and reach to the peak during the 10 and 15 years of age. Food hypersensitivity (food allergy) is due to immunological reactions as a result of the food sensitivity or food additive that occurs in some of the patients with gene susceptibility [11]. In contrast, none of the IgE mediated food allergies are called food intolerance. However, the most important items of the clinical features of the food-allergic reactions occur in the gastrointestinal tract (GI), but the other organs, such as the respiratory tract, the skin, the eye, systemic anaphylaxis or even central nervous system (CNS) may be involved. The GI tract is a special organ because it is constantly exposed to harmful substances. The GI mucosa is challenged daily with thousands of compounds. Particularly, it is bombardment by potential allergens, such as food components (e.g., food proteins or glycoproteins) and other antigens such as bacterial, fungal, viral and worm antigens), drugs and chemicals, pollens, house dust mites, and any other materials entering the GI tract. In general, M cells in the GI mucosa (which is an epithelial cell with microflora that transports macromolecules) are specialized for the uptake of particulate antigens. Therefore, pathologic immune reactions become very high, aggressive and disruptive in this system [12].

The symptoms of the food allergy that is manifested in the gastrointestinal system are dependent on the site of mucosal reactions. Therefore, the symptoms can be observed in patients with a focus on four categories, including; 1) Oral allergy syndrome (e.g. swelling of lips and tongue, pharyngeal itching and laryngeal edema), 2) gastric reactions (e.g. gastroesophageal reflux, nausea, and vomiting), 3) small intestine problems (e.g. abdominal pain, malassimilation, and vitamin deficiency), and 4) colon and rectal involvement (e.g. diarrhea, obstipation, and even fecal blood loss) , Allergic patients commonly suffer from gastrointestinal and skin diseases. But urticaria, atopic dermatitis, angioedema, asthma, rhinitis, and anaphylaxis in severe cases were seen with gastrointestinal symptoms. The interval time between the onset of clinical symptoms and food challenge may be varied from a few minutes to many hours. Generally, earliest reactions occurring within 5-15 minutes, involve the lips, pharynx, stomach, and duodenum. This is a classical IgE-mediated reaction. Whereas the late reactions are occurring between 24 and 48 (delayed reactions) after food allergen challenges that are often related to small or large intestine involvement. Most of the common food allergens associated with gastrointestinal allergy including; Cows' milk, hazelnuts, peanuts, eggs, meat, fish, crustaceans, and cereal grains, are named "big-eight food allergens". These allergens are responsible for IgE- mediated food allergies, which almost are the reason for 90% of the food allergies. The prevalence of food allergies is 6-8% in infants, 2-4% in older children and adults with a real food allergy [11].

To make a diagnosis of the allergies, other factors such as the effect of non-immunological phenomena, the use of certain medications, the history of the disease of the child and the parents of the patients should be evaluated. Sensitivity to an allergy may be different in patients, and the diagnostic tests along with clinical symptoms should be able to help the diagnosing the severity of allergy in patients. It should be noted that during the history, the presence or absence of the non-allergic symptoms has also been investigated, and in case of the allergic history of children, the main details are asked in below questions [6].

Are the symptoms of patients in clinical complaints associated with a major allergen (Big Eight Foods)? Do the patients introduce their starting allergen? How long it takes that the symptoms be apparent after contact with an allergic agent? Are symptoms bilateral? Is there a family history of atopic diseases? How much did the patient respond to the previous treatments? Are the symptoms continuous or intermittent? How much is their severity? Also, the time or number of days when the symptoms are seen in children, their absence from school or admission to the hospital should be investigated [8].

Mast Cells Activation and Brain

The persistence of the mast cells is in a different part of the brain. The meninges during evolution enter the brain through blood vessels. Moreover, the mature mast cells can migrate from peripheral blood into the brain. In spite of the small numbers of the mast cells inside the brain, activated mast cells can play an important role in the neuroinflammation process. The majority of the mast cells are located in the abluminal areas of the blood vessels, where they can communicate with the neurons, glial cells, and endothelial cells (EC). The actual number of the mast cells inside the brain tissue is not easily calculated, because it is altered by some factors such as species and age. However, it has been reported that the brain mast cells are not a lot inside the brain and mainly are from the Tryptase-Chymase phenotype. Furthermore, their quantity and distribution and the impact of the environmental stimulating factors such as trauma and several stresses probably change the allergies. The mast cells are known as an immune gate of the brain because they function as the effector cells during the communication between the nerves, arteries and the immune system. They are located in the BBB of the brain tissue. Furthermore, it is proposed that during the neuroactive-stored and the newly synthesized mediators' release, the activated mast cells interact with the brain cells including astrocytes, microglial cells, and blood vessels [7].

The mast cells also exist inside the hypothalamus, and they are connected to the limbic system, which regulates the emotions. The mast cells are responding to several chemical stimuli, such as allergens, antigens, complement factors, neuropeptides, drugs, and even trauma and contribute to the degranulation of their toxic granules in the inflammatory reactions. The mast cells are developed in most of the body tissues and their function is well known in the allergies and anaphylaxis. The Cross linking between FCεR and Immunoglobulin-E (IgE) has the most important route of mast cells activation. However, it is shown that they are activated by various IgE-independent mechanisms, such as TLRs, cytokines receptors, complement, and

tropomyosin. The mast cells play a central role in the responses to the early innate immune system during the trauma and induction of the inflammation after tissue damage. They are also contributing to the end-organ injuries after trauma associated with the activation of the complement system. The mast cells are the earliest responding cells in the innate immune defense that act as a catalyst [5,7].

Basically, the mast cells are highly heterogeneous. This means that they are very various in morphology, stored mediators and response to the activators. Upon mast cell activation, both preformed and newly synthesized mediators such as histamine, serotonin, trypase, and heparin are secreted. Besides, lipid mediators, such as prostaglandins, leukotrienes, growth factors, and other arachidonic acid metabolites are also synthesized after mast cells' stimulation using IgE, which is called a synthetic mediator. Finally, in the late phase of mast cell stimulation, several cytokines and newly mediators such as IL-3, IL-4, IL-5, IL-9, IL-13 and tumor necrosis factor-α (TNF-α) are synthesized and released. The released IL-6 and TNF-α by mast cell play an important role in the elimination of the bacteria in the sepsis flow. The release of histamine may be responsible for capillary of permeability; also it's the low dose of the injection, which causes extreme hypotension. The mast cells effect on the basal membrane so, BBB damage leads to aggravated, brain edema, prolonged extravasation, and hemorrhage [10]. Therefore, the mast cells should be investigated outside of the inflammatory responses of the neurovascular unit. The brain mast cells' moderate functionality in the inflammation process is caused by brain ischemia and neutrophils accumulation. Also, degranulation of the mast cells may be due to the perivascular edema formation during the brain ischemia.

Mast cells are prominently located in the perivascular area and have fast-acting vasoactive and protolithic agents, inside the brain. Figuring out how the mast cells disrupt epithelial barrier functions in the BBB, helps to the understanding of the mental events of the brain's neurodegenerative. There is a coherent network called neurovascular unit, including venous, prevascular cells astrocytes, microglial neurons, and other cells. Firstly, indirectly and through interaction with glial cells and neurons lead to release the molecules such as IL-6, IL-1, and nitric oxide. Secondary, directly and through releasing of mediators such as histamine and chymase and TNF-α. In particular, mast cells are an important source of histamine and only cells that store TNF-α are synthesized, inside the brain. During the neuroinflammation, mast cells may affect the BBB as a catalyst [2].

Mast cells contribute to tissue damage in two ways inside the brain. Therefore, this might be due to the toxic mediator release, which develops harmful consequences in the brain function. So, its surrounding area will create tissue inflammation. Mast cells exist in the vital areas of the brain, such as autonomic nervous system and emotional (e.g. diencephalon and Broca area). They are activated by environmental, infectious, or stress factors and lead to the development of the local brain allergies or focal encephalomyelitis in the CNS. The stress is an important factor that activates brain mast cells and leads to damage in the BBB [9].

Prenatal stress increases the risk of autism. In the case of children with autism, anxiety is increasing and they cannot control their stress properly. Prenatal or perinatal stress, which is complications during the pregnancy, may also contribute to developed autism through the abundant CRH abandonment. Maternal CRH is not able to cross the placenta and large amounts of CRH are produced by pairing themselves in response to external or intrauterine stress. Interestingly, CRH can degrade BBB by activating mast cells and increase intestinal permeability. IL-9 derived from mast cells induced intestinal permeability and makes children more susceptible to oral antigens, which makes toxic brain damage to be worse in the infant. Perinatal mast cell activation destroys GBB (Gut-Blood-Brain) barrier by releasing cytokines in response to allergic or non-allergic initiators. Therefore, neurotoxic molecules allow entering the brain, leading to inflammation of the brain. As a result, these molecules contribute to the pathogenesis of autism. This process gets worse with the genetic, metabolic, allergic, autoimmune, environmental or other factors [11].

Furthermore, corticotropin-releasing hormone (CHR) that is released under stress conditions can activate mast cells directly by non-immunologic mechanisms. In this way created a mast cell-dependent BBB disruption. Recently it is reported that FCεRI, which is typically expressed only on mast cells and basophils, has been identified on the surface of the neuronal cells. Most importantly, it shows that the allergic stimulating factors may even effect on the neurons directly and exacerbate the BBB disruption. This destruction, allows the antibodies to enter the neural tissue directly from the blood due to the presence of a damaged blood-brain barrier [10].

The most abundant sources of the mast cells are found in the brain and particularly diencephalon hypothalamus, which are involved in the regulation of behavior and language development. Hypothalamus is a part of the diencephalon that has secondary communication between different areas of the brain. It connects the limbic system to emotional regulation. The increased neurotensin serum levels associated with autism. On the other hand, the most focus of the neurotensin receptors is found in the hypothalamus and Broca area that regulates the speech. These receptors are disrupted in a large number of neurodegenerative diseases such as autistic children. The mast cell stimulation induced by neuro-peptides could lead to DNA and mitochondrial release into the extracellular spaces, which promotes the neuroinflammation conditions. Corticotrophin is a hormone that is secreted by hypothalamus under stress conditions and stimulates brain mast cells with neurotensin. These events, lead to a focal allergy and excessive neurotoxicity inside the brain cells. Mast cell and microglial interactions are very important in the induction of neuroinflammatory diseases. Functional gastrointestinal symptoms such as abdominal pain, bloating, distension, diarrhea, and constipation often have been observed in autistic children. Although, the reasons for this issue have not been well understood. Furthermore, increase secretion of MCP-1 and CSF inside the brain of children with autism were reported. MCP-1 is a strong chemoattractant for mast cells. Therefore, any toxic factor that changes the bacterial gut storage, will eventually lead to changes in the immune-neuroendocrine network [9].

Mastocytosis is a disorder with a prevalence of 1 to 4000 in children, which is related to the mast cell activation and proliferation in the skin and other organs. Mastocytosis may be the result of skin reactions. Food allergies that are often accompanied by a negative SPT and lack of food intolerance particularly in children have shown behavioral signs of autism. The intensity of the skin is associated with the deterioration of their behavioral symptoms. Several peripheral mediators, with peripheral, intestinal or brain origin, including histamine, prostaglandins, proteases and VEGF other chemokines and cytokines such as IL-6, IL-8, IL-9, IL-13, and TNF-α can activate the mast cells. Bacterial lipo-polysaccharides via TLR-4, lead to mast cell activation and mediator release. TLR-4 is on the surface of mast cells, which is selectively produced and secreted TNF-α. Mast cells may have a crucial role in the pathogenesis of allergic diseases by secreting the inflammatory mediators [11].

But they have also an important role in the inflammation, innate and acquired immune responses. Mast cells-neuron interactions occur in the gastrointestinal tract. Accordingly, mast cells involved in hypersensitivity and inflammatory processes lead to an increase in the permeability of intestines. This may be an explanation for the gastrointestinal symptoms in autistic patients. This suggests that there are high levels of macrophage chemoattractant protein-1(MCP-1) in the CSF and microglial cells of children with autism. MCP-1 is a potential chemoattractant for mast cells.

Brain mast cells and glial cells

Microglial cells are the innate immune cells of the brain that are involved in a large number of neuropsychiatric diseases like autism. Immune cells, such as the microglial cells that enter the brain, are inseparable parts of the evolution and function of the brain. Recently, the abnormal growth of the microglial cells and their activation has been reported in the patients with ASD. Although, researchers have obtained some information about the molecular mechanism of the relationship between the mast cells and peripheral nerves. Nevertheless, non-immunological interaction between the mast cells and the neurons is not yet well defined, and this suggests that it may be similar to these interactions between mast cells and CNS neurons. Researchers suggest that the simultaneous presence of both mast cells and neuronal cells are essential for the interaction of the immune system and neurons. The cytokine secretion and inflammatory responses inside the brain are controlled by the brain's microglial cells. These cells are a presence in the CNS, and due to having a phagocytic scavenging activity, they are likely to have similar functions associated with the environmental macrophages [8].

Microglial cells are effector cells involved in bout neuronal and immunological functions. In physiological situations, microglial cells tend to rest and under neurotrophic conditions such as synaptogenesis, neurogenesis is involved via inflammatory cytokines. However, when the brain tissue is damaged and the hemostasis microenvironment is disrupted, the microglial cells are switched from homeostasis to diseases and secreted several proinflammatory cytokines, chemokines and reactive oxidants that are involved in a variety of immune and inflammatory responses [1].

The Cross-talk between mast cells and microglial cells in a neuroimmune axis suggests that this character can exacerbate inflammatory responses and contribute to the formation of the acute symptoms of neurodegenerative chronic diseases. The mast cell tryptase is a potential inducer of the microglial activity and PAR2 receptors. Regarding the distribution of the different forms of this cell connection results in the release of proinflammatory cytokines including TNF-α, IL-6 and ROS and plays an important role in neurodegenerative diseases such as autism. IL-6 induced IL-13 production in mast cells and it also affects the expression of TLR4 /TLR6. Also, under inflammatory conditions, proinflammatory mediators like TNF-α up-regulate the expression of PAR2 on the surface of mast cells. In addition, upon mast cells activation, some of the chemokines such as CCL5 also are upregulated and overexpressed under the inflammatory conditions. Cell adhesion molecule-1 (CADM-1) is another molecule that makes the interconnection between mast cells and feeling neurons. CAM1d, which is an isoform of CADM1, is expressed in the mature neurons, probably plays an important role in the promote mast cell neuron interaction. Also, the released neuropeptides such as substance-P, neurogenic and growth factor can be enabled to activate the functions by being attached to the mast cell membrane. The mast cells' activation by substance-P and degranulation results in the release of some cytokines and chemokines such as MCP-1, IL-8, and CCl-5. The IL-4 (Th2 cytokines), also increased the expression of the neurokinin-1 receptor on the mast cells that led to an increase in mast cell sensitivity and reached to the SP. Mast cells' products such as histamine and serotonin enter into the adjacent neurons, which will lead to a change in the inner environment of the neurons. Some other molecules (such as C5a. R, that is, CXC chemokine receptor and TLR-4) may be involved in the interaction between the microglia and the mast cell. This wide variety of two-sided connections between the two cells strongly suggested that mast cells and microglial contribute to neuroinflammation and neurodegeneration in the CNS. Also, changing the susceptibility of the neurons has been shown by the mast cell heparin degranulation. In fact, intracellular heparin as a pharmacological component might function as a blocker or an inhibitor of releasing intracellular calcium. Thus, this leads to the inhibition of the neuronal responses. All the above information, demonstrated a new connection between the neuron-mast cells that if they would have disrupted the physiological order between them, they might have had one of the aggregative or even etiologic factors in autism disorders [3].

The histamine, which is released from mast cells, subsequently interacts with microglial cells, because microglial cells have all of the histamine receptors (e.g. H1R, H2R, H3R, and H4R). Signaling via these receptors sustains the expression of the prion-inflammatory genes (e.g. IL-6, Il-1β, TNF-α), which is associated with the neuroinflammation and neurodegeneration in the CNS [11].

Astrocytes inside the brain: The interaction between astrocyte and a mast cell is feasible because both of them challenge each other in the perivascular area. Moreover, during the selected conditions used in the co-culture of astrocyte and mast cell, many mediators such as histamine and leukotrienes are released. Also, mast cell-astrocyte interaction leads to induction of the product of chemokines and cytokines such as IL-6, TNF-α, MCP-1, and CCL5. The IL-33 has been reported to be as an alarming cytokine that produces upon astrocyte injury, which has been occurred in the presence of neuroinflammation in the CNS. IL-33 activates the mast cell and microglial that leads to some changes in the innate immune response. Furthermore, mast cells can be activated for IL-6, IL-8, and IL-13 production. The H1R, H2R, H3R receptors are expressed on the surface of the astrocytes too. A similar phenomenon has been seen in the cell culture of human astrocytes, as histamine can stimulate MMP-9 production via H1R. Besides, the astrocytes induce neurotoxicity inside the brain tissue by nitric oxide production. There is much experimental information that indicates that NO is associated with autism [3].

Pro-inflammatory cytokines

Cytokines are pleiotropic molecules that transmit the intracellular signals and play important roles in the inflammatory responses. They are large proteins with a 15- 25 KDa weight, which are released mainly from immune cells such as leukocytes, macrophages, lymphocytes, microglial cells, and astrocytes. Cytokines are usually produced in physiological conditions at lower levels, but in the pathologic conditions, it will be increased up to 100 times the natural or physiological conditions. For example, when the micro-environment in the CNS undergoes to tissue damage, trauma, infection, or ischemic attacks, cytokines are produced by larger microglial cells [5].

They are mainly divided into two groups; pro-inflammatory cytokines, including IL-1β, IL-6 and TNF-α, and anti-inflammatory cytokines such as IL-4 and IL-10, which facilitates or inhibits inflammatory responses respectively. Different conditions such as

inflammation, infection, or immunological changes, can produce cytokines, which are mainly involved in the processes such as repairing damaged tissues and returning to homeostasis. The brain receives immune signals through cytokines that are transmitted by the blood-brain interface (BBI) [6].

Pro-inflammatory cytokines and the cytokines that cause neuro-inflammation are involved not only in inflammatory responses but also in neurogenesis and neuroprotective processes. As an example, in case of persistent stress that is associated with the release of the pre-inflammatory cytokines, it causes chronic neuroinflammation, which contributes to the depression. Hippocampal glucocorticoid receptors (GR) and their relation with the Hypothalamus-Pituitary-Adrenal (HPA) axis have a strong interaction with pro-inflammatory and neuro-inflammatory cytokines. Neuro-inflammation causes an imbalance between the oxidative stress and antioxidant system, which is associated with the depression [5].

The brain is evaluated as an immune-privileged area and in a neuro-inflammation condition, a large number of cytokines pass through the BBB. For the first time in 1983, Blatteis noticed that the cytokines were transmitted from the brain. In the early stages of evolution, the activity of pre-inflammatory cytokines may have endemic effects on the brain. Prenatal the contacts of the pre-inflammatory cytokines and spatial memory lead to damaged and destroyed nerve cells and gliosis inside the hippocampus [4].

Increasing the inflammatory mediators does not necessarily lead to damage in the normal tissues. However, the primary goal of inflammation is the defense and preservation of the neuronal integrity in the CNS, which has been damaged [3]. Although the sustained release of the pro-inflammatory cytokines may be one of the most important features of the distinction between systemic inflammations from neuro-inflammation. Pro-inflammatory cytokines such as IL-1-β, IL-6, TNF-α, initially carry out inflammatory processes in the nervous system.

Many studies have shown that immune factors such as TNF-α, IL-1β, and IL-12 have been increased in the patients suffering from ASD. Additionally, CSF level of pro-inflammatory cytokines has been also increased in the autism. Recent studies have shown the microglial cells' function that has CNS-based immune cells in postnatal evolution. Today, the hypothesis that microglial cells play a role in psychiatric disorders is progressively being strengthened. It has been shown that serum endotoxin level as a non-specific symptom is significantly higher in patients with chronic infections.

IL-6, IL-1β: In children with autism, increased expression of IL-6 gene inside the brain cells and high levels of TNF in CSF have been reported. While it seems that in the physiological conditions, the pro-inflammatory cytokine IL-6 has neuroprotective effects, it plays an important role in the proliferation and survival of the NSC. Furthermore, increased levels of IL-6 in inflammation may be related to neurotoxicity, which probably induces IL-1β changes in connection with IL-6 and TNF-α. It has been shown that IL-1β reduced the hippocampal Neuronal Stem Cell (NSC) proliferation and correlates with neurogenesis in the brain, especially in the hippocampus [4].

TNF-α: This type of cytokine can stimulate and inhibit neurogenesis, which depends on the involved receptors' type. The involvement of TNF-R1 suppresses NSC proliferation while increasing the activation of TNF-R2 proliferation and the survival of newly synthesized neurons. TNF-α may also have a dual effect. The harmful or protective effect depends on the recipient's subtype to an attached thing, level, and timing of the release of the cytokine. TNF-α is one of the most important pro-inflammatory cytokines that inhibit neurogenesis [3].

Histamine: H1R, H2R, H3R receptors are presented on the NSCs that is thought to be histamine neurogenesis effects.

Serotonin: Neurons and mast cells are responsible for the production of serotonin in the CNS. Although these mediators exist only in the low concentrations in the mast cells, 20-40% of serotonin is originated from the mast cells.

Neuro-tensin: There is a neurotensin peptide inside the brain and gut. Studies have shown that the levels of the peptide increase significantly in the serum of children with autism. Neurotensin can cause proliferation of the lymphocytes, stimulate T lymphocytes, increase levels of IL-1 from macrophages, and activate mast cells. It is also capable of stimulating mast cells to release extracellular mitochondrial DNA [6]. This kind of DNA is significantly increased in children with autism. Neurotransmitter stimulates the mast cells to produce mitochondrial adenosine triphosphate and DNA. Both of these molecules are increased in the serum of children with autism. These mitochondrial compounds initiate a series of allergic reactions inside the brain. TGF-β1 inhibits the function of mast cells, which its plasma level is low in children with autism. Moreover, mast cells express viral TLR3, which is activated by the double-strand RNA. It can lead to induced IL-6 and TNF-α secretion, without mast cell degranulation. The ability of some viruses such as retrovirus has been reported to activate mast cells directly. Environmental toxins are associated with developmental neurotoxicity. Polychlorinated biphenyl (PCB) and mercury are associated with autism and activate mast cells. Mast cells are stimulated to selectively drop some mediators by non-allergic initiators. For example, the corticotropin-releasing hormone (CRH) releases VEGF selectively. The CHR is typically secreted from the hypothalamus, but it also can be secreted from the extremity of the extracranial nerves, where the pro-inflammatory effects are applied. CHR has synergistic effects with NT for increased permeability. Many studies indicate that NT levels increase in children with autism [5].

BBB Permeability

Mast cells are located in the CNS and can migrate through the BBB. Also, in places that are as a brain barrier, they endanger the health of the CNS. Mast cells can be reacted with some NUV compounds such as microglial cells, neurons. It will exacerbate the breakdown of the BBB. Some mast cells mediate such as histamine and TNF-α, which have vasoactive properties. Mast cells may also release matrix-degrading molecules such as proteases. Due to the properties of the mediators derived from the mast cells, it is hypothesized that they can affect BBB permeability. Mast cells may also affect the integrity of BBB through MMP. MMPs are a large family of proteolytic proenzymes, which, when activated, affects most protein compounds in ECM including collagen, elastin, fibronectin, and vitronectin. Thus, the enzymatic activity of MMPs is very strict and is regulated by TIMP inhibitors. The activity of the mast cells can affect gelatinase activity. In addition, the chymase derived from these cells regulates MMP9, MMP2 activity. Both of these mediators damage the BBB dam by destroying tight junction connections. Furthermore, mast cells stimulate infiltration of neutrophils, which themselves are an important source of MMP-9 production. MMP-2 and MMP-9 both are proteolytic gelatinase enzymes, which have a central role in compromising the integrity of BBB after ischemia [5].

TNF-a induced mast cells to produce MMP-9 and increase the permeability of BBB. Also, it increases the level of IL-6, which is

involved in the degeneration of monolayer endothelial cells. TNF-α also increases the expression of ICAM-1 and VCAM-1 on the surface of the endothelial cells of the small brain vessels of the rat. Therefore, TNF-α interferes with ICAM-1 in the brain through the binding of neutrophils to the ICAM-1 [3]. The upregulation of ICAM-1 and failure of BBB tolerance in the entry of leukocytes into the brain, leading to inflammatory disorders of the brain such as Multiple Sclerosis. Besides, brain histamine plays a role in regulating BBB permeability. Increased levels of NT neuropeptides have been seen in young patients with ASD. Direct mast cells stimulation by neuropeptides leads to the release of mitochondrial DNA and ATP into extracellular space, which protects neuro-inflammation conditions using the stimulation of the mast cells to release inflammatory cytokines.

Additionally, mitochondrial compounds are increased significantly in the serum of the children with autism. The pro-inflammatory cytokines such as TNF-α, IL-6, and GM-CSF are grown significantly inside the brain tissue of children with autism. Also, levels of MCP-1, a strong chemoattractant for mast cells, are high inside the brain tissue and CSF fluid in the children with autism [10]. While many studies point to the negative effects of the presence of cytokines, they also have a lot of beneficial and neuro-immune effects. Physiological levels of inflammatory mediators released by mast cells and glial cells, not only have an immunological function, but also have a promotive role in neurogenesis in the CNS. Serotonin, IL-6 and IL-1β play neuroprotective roles and maintain the integrity of BBB. The increased levels of these mediators have decisive effects on the neurons and BBB integration and they associate mast cells with a variety of brain disorders [7].

Brain neuroinflammation

Neuroinflammation is distinct from the inflammation of other tissues due to its unique CNS properties. Microglial and mast cells are two main human immune cells that are involved in the Neuro-inflammation. In cases where these cells undergo dysregulation, they affect the correct implementation of the tissue reactions. Neuro-inflammation has an association with various types of reactive oxygen species including superoxide, nitric oxide, and hydrogen peroxide [9].

On the other hand, natural interactions between the immune system, endocrine, and the nervous system have also been proven. The central nervous system nerves to the primary and secondary organs of the immune system and endocrine system via direct axonal. The immune cells can communicate with the release of cytokines or neuro-transmitters and transmit signals amongst the nervous, endocrine and gastrointestinal systems. Immune responses depend on the genetics, age, gender, and interactions between the immune and endocrine systems of people, previous and current contacts with environmental stresses, which included psychological stress (neuro-immune interactions). Inversely, immune responses can modify the nervous and endocrine system functions. Interactions of the endocrine, nervous and immune system are collectively known as the immune-neuroendocrine network (INEN) [6].

Many functional aspects of the peripheral nerves are strongly dependent on the activity of neurotrophins. Neurotrophins (nerve growth factor and brain-derived neurotrophic factor) have all kinds of immune cells that are involved in the pathogenesis of allergic diseases. The immune cells can produce neurotrophins in all conditions. Neurotrophin levels and neurotrophic activity increase significantly in allergic conditions. Microglial cells express all 4 histamine receptors including; H1R, H2R, H3R, and H4R. Through these receptors, they are stimulated to produce TNF-α, IL-1β, and IL-6. Interactions between mast cells and astrocytes are also possible because both of them interact with each other in the pre-vesicular areas.

Neuroendocrine hormones released in the stressful conditions can lead to a loss in the immune regulation, followed by a change or an increase in the production of cytokines [9]. Imbalance in the production of cytokines can be the reason of atopy and autoimmune diseases or reduce host defense associated with the presence of mast cells. There are various transfusion materials include endorphin, norepinephrine, acetylcholine, substance P and vasoactive intestinal peptide (VIP), glucose, insulin, cytokines, growth factor, and other mediators in the neuroendocrine and immune system (NIE). Stress responses and induction of conditions that lead to cytokine imbalance are capable to activate the hypothalamic-pituitary-adrenal (HPA) axis and begin the nervous system symptoms. Disorders that cause abnormal reactions to immune function are caused by the NEI network. These disorders are caused by excessive production of the neuropeptides and cytokines in allergic diseases such as allergic rhinitis, atopic dermatitis, digestive system allergies, and asthma.

Synaptic disorders may lead to neuronal damage and inadequate neurotransmission prior to cell death. Therefore, synaptic dysfunction is evaluated as a neurodegeneration factor. Cytokines may be physiologically important for the induction and maintenance of the synaptic ductility and memory mechanisms. For example, the expression of IL-6 and IL-1β gene in the hippocampus following LTP induction is markedly upregulated. This explains the physiological role of them [2]. However, increasing the expression of the cytokines during the neuro-inflammation may damage the synaptic plasticity. Increased levels of IL-1β and TNF-a can inhibit LTP. LTP, which is one of the forms of synaptic plasticity that was seen in the hippocampus and increases the synaptic efficiency, that plays an important role in the education and memory process.

Neurodegeneration: Probably neuro-degeneration affects the neuronal apoptosis directly by producing high levels of inflammatory molecules. Therefore, inflammatory molecules accelerate neuro-degeneration conditions. Also, during the neuroinflammation, activated mast cells may be effective in accelerating neuro-degeneration. The activation of mast cells leads to delayed neuro-degeneration in a mixed culture of neuro-glial cells. The rapid release of mast cell mediators cannot be sufficient to damage the neurons alone. As a result of the release of mast cell mediates, no severe neuro-degeneration has been found. Released TNF-α from mast cells, probably releases nitric oxide from astrocytes in conjunction with other cytokines, which leads to nephrotoxicity.

Neuroinflammation and Psycho-neuro-immunology: Meanwhile, in the aspect of clinical medicine, neuro-inflammation is particularly important for immunologists and allergists. There are also correlation allergic responses associated and severe tissue damage and this caused severe and irreparable damage for hemostasis, health, and quality of life [9]. Therefore, the neuro-immunologists and other researchers have made many efforts to reach a better understanding of these complex interactions and to develop new strategies or drugs that will prevent and reduce the neuroinflammation and neurodegeneration in the CNS. Neuro-inflammation can increase the sensitivity of the brain to stress and thereby enhance attention, vigilance, behavior and memory formation in the patients. Thus, neuropsychiatric disorders due to the stress associated with a series of complex inflammatory cytokines. Even though the inflammation is primarily intended to protect the tissue and it has a beneficial effect, but chronic stable neuro-

inflammation results in the harmful effects in this tissue. As these conditions make changes in BBB structure, brain parenchyma, and neuronal hyper-excitability and eventually, neuron death occurs [11].

Excitotoxicity: Excitotoxicity is the death of neuronal cells caused by excessive or prolonged activation of the glutamate receptors. Defective glutamate removal by glial cells results in increased levels of glutamate, which leads to increased glutamate receptor stimulation. Neuro-inflammation-related cytokines, particularly TNF-α and IL-1β, can affect glutamatergic receptors. In physiological conditions, TNF-α is important for synaptic plasticity. Increased levels of TNF-α can inhibit glutamate receptors on astrocytes, which increases the concentration of glutamate in the CNS parenchyma [10]. Many studies have shown that TNF-α has the potential to increase the glutamate neurotoxicity and also increase excitotoxicity in the hippocampal neurons.

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