Autism and Food Allergy

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Introduction

e prevalence of food allergy is up to 5% in the rst year of life, and autism spectrum disorders (ASD) (6.0/1,000) is predominant in early childhood. e 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 neuroin ammation and behavioral changes in autism. Today, we know that food allergies e ect 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 neuroin ammation 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 (speci cally gluteomorphin and casomorphin) can mimic some chemicals in the brain called endorphins.

Despite the fact that food allergy a ects 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 su ering from Child food allergy [3]. e 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. is chapter focuses on the relationship between autism and child food allergies. To get started it is important to de ne 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) Neuroin ammation 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 neuroin ammation issue in various neurodegenerative diseases. e in ammatory response that occurs in the brain is called neuroin ammation [4]. Microglial cells and astrocytes are the main cells that respond to the released mediators of the anti- in ammatory cells and are getting hurt or injured. Brain mast cells are an important source for producing anti-in ammatory molecules. ey 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. e increased level of these mediators during the in ammation has negative e ects on the neurogenesis, neurodegeneration, and permeability of the BBB inside the brain tissue. Furthermore, the amount of mitochondrial extra-cellular compounds and anti-in ammatory cytokines including IL-6, TNF-α and GM-CSF and chemoattractants such as MCP-1 are signi cantly higher inside the brain tissue of patients su ering 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 a ects the brain. e gastrointestinal symptoms such as abdominal pain, diarrhea, and constipation are o en 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. e 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 e ective nutritional interventions in high-risk populations.

Mast cells are the rst responder cells inside the brain, which can initiate and develop the immune responses in the nervous tissues. ey 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 in ammatory 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].

e presence of neurotensin, which is a neuropeptide inside the brain, contributes to the trigger severe in ammatory reactions inside an autistic brain. e brain mast cells are known as "immune gate to brain" cells. ey are abundantly seen in the hypothalamus. e brain mast cells in CNS are closely interconnected with the neurons, which is an important part of the beginning of a neuroin ammation process inside the brain. Mast cells' function in the induction of neuroin ammation, 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].

In ammation is an innate immune system response that has a protecting role and usually leads to elimination of the destructive

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

e 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-in ammatory cytokines may have stable harmful e ects on the brain. erefore, the following prenatal exposures to anti-in ammatory cytokines damage the hippocampus and spatial memory. Besides, loss of nerves and nerve damage in veins has been observed.

erefore, the in ammatory cytokines and cytokines, which cause neuroin ammation, are involved in both the in ammatory responses and neuroprotective processes. During the constant stress conditions, the anti-in ammatory cytokines have been released, which lead to chronic neuroin ammation that is a promotive factor associated with autism [8-11].

Clinical Manifestations of Food Allergic Disease

According to the clinical ndings and Coombs and Gell classi cation, 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. e GI tract is a special organ because it is constantly exposed to harmful substances. e 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 micro ora that transports macromolecules) are specialized for the uptake of particulate antigens.

erefore, pathologic immune reactions become very high, aggressive

tropomyosin. e mast cells play a central role in the responses to the

But they have also an important role in the in ammation, innate and acquired immune responses. Mast cells-neuron interactions occur in the gastrointestinal tract. Accordingly, mast cells involved in hypersensitivity and in ammatory processes lead to an increase in the permeability of intestines. is may be an explanation for the gastrointestinal symptoms in autistic patients. is suggests that there

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

Pro-in ammatory cytokines and the cytokines that cause neuro-in ammation are involved not only in in ammatory 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-in ammatory cytokines, it causes chronic neuroin ammation, 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-in ammatory and neuro-in ammatory cytokines. Neuro-in ammation causes an

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. erefore, TNF-α interferes with ICAM-1 in the brain through the binding of neutrophils to the ICAM-1 [3]. e upregulation of ICAM-1 and failure of BBB tolerance in the entry of leukocytes into the brain, leading to in ammatory 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-in ammation conditions using the stimulation of the mast cells to release in ammatory cytokines.

Additionally, mitochondrial compounds are increased signi cantly in the serum of the children with autism. e pro-in ammatory cytokines such as TNF-α, IL-6, and GM-CSF are grown signi cantly 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 uid in the children with autism [10]. While many

in ammation results in the harmful e ects 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-in ammation-related cytokines, particularly TNF-α and IL-1β, can a ect 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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