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Review

Autism and Il-17A Relationship: Why Does Fever Reduce Autism Symptoms?

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ABSTRACT

Autism spectrum disorder (ASD) is a neurological disease that manifests itself with behavioral abnormalities, repetitive behaviors, and socialization problems due to brain development problems. Maternal immune activation (MIA), which occurs as a result of an infection during pregnancy, causes some developmental disorders in the brain of the fetus. Immune response to infection in the mother causes some cytokines such as interleukin-17 (IL-17) to be released, which in turn causes brain damage by affecting the cell differentiation in the fetus. This damage can affect different parts of the brain or systems, leading to ASD symptoms. Features seen in ASD have been associated with the primary somatosensory cortex dysgranular zone (S1DZ) region of the brain and the locus coeruleus/norepinephrine (LC/NE) system. Interestingly, children with autism had a reduction in autism symptoms during fever. It has been observed that children with autism who have difficulty in socializing and who do not make eye contact make eye contact during a fire and their movements become calmer. Related to this issue, it has been observed that some cytokines produced during fever, an inflammatory response, may affect brain function, thereby temporarily suppressing autism symptoms. The purpose of this review is to explain the relationship of autism spectrum disorder with IL-17A and fever through their mechanisms. In the review, the emergence of autism, its general mechanism, the related S1DZ region and LC/NE system in the brain, and why ASD symptoms disappear during fever were discussed.

Keywords: Autism spectrum disorder, fever, interleukin-17, maternal immune activation.

Cytokine comes from the Greek words"cyto" meaning cell and "kinos'' meaning movement. Cytokines are small proteins released by cells to regulate the growth, maturation and responsiveness of certain cell populations. Cytokines mostly play a role in the regulation of the immune system. They can have a positive effect by stimulating the immune system to fight a foreign pathogen or attack tumors. In addition, patients with multiple sclerosis (MS), have a beneficial effect by reducing the immune response as cytokine interferon decreases neuronal inflammation. On the other hand, when their expressions cause inflammatory diseases, they can have negative effects such as rheumatoid arthritis, asthma, and Crohn's disease.[1]

The Interleukin-17 (IL-17) family is also a subset of cytokines.[2] IL-17 was discovered in the 1990s and turned out to be a pleiotropic cytokine, that is, it has many different functions. IL-17; Th17 (T helper 17) cells can be produced by a wide variety of immune cell populations, such as CD8 + T cells (cytotoxic T cells), natural killer (NK) cells. The unique effector functions of these cell subsets allow IL-17 to have very different functions.[3]

There are 6 different members of the interleukin-17 (IL-17) family that have been identified. These are IL-17A (also called CTLA8), IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25) and IL-17F.[2] IL-17A, the most widely studied cytokine of the interleukin-17 family, plays important roles in host defense against microbial infections

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and the development of inflammatory diseases. Immune cells that produce IL-17 provide rapid release of IL-17A in response to pathogens or tissue damage. For example, γδ T cells (gamma delta T cells) use pattern recognition receptors (PRRs) such as dectin-1 and Toll-like receptor 2 (TLR2), which allow the production of IL-17 in response to encounters with bacteria. receptors) express. IL-17A is also produced by a subset of CD8 + T cells that can participate in host defense against viruses and contribute to autoimmunity.[3] IL-17A promotes inflammation by inducing various pro-inflammatory cytokines and chemokines, increasing antibody production, and activating neutrophils and T cells. IL-17 receptors (IL-17R) are involved in the regulation of IL-17 signaling.[4]

Interleukin-17A is also known to be one of the main triggers in various inflammatory and autoimmune diseases. The abundance of this cytokine is associated with pathological conditions. High levels of IL-17A have been found in individuals with diseases such as MS, psoriasis, asthma.[2]

AUTISM SPECTRUM DISORDER (ASD)

While ASD is a rare childhood disorder that has not been studied much; has become a very common, researched and lifelong disease in the last 50 years.[5]

Autism spectrum disorder is a life-long disorder that starts before the age of three, has little social interaction, causes limited and repetitive behavior, and prevents the development of the brain. Compared to typically developing individuals, in individuals with ASD, brain development is accelerated early in life, resulting in altered connections in the brain.[5]

OSB is characterized by key features in two areas:

1. Social behavior.

2. Restricted, repetitive sensory-motor behavior.

People with ASD have problems with sensory-motor behavior and socialization. They overreact to certain events and give different meanings to objects. In short, these people have difficulty controlling their emotions and reactions. Nervousness and aggression are more common in ASD than other developmental disorders.[6]

Genetic, neurological, immunological and environmental factors play a role in the development of ASD. A study published in 2016 stated that 74-93% of the risk of ASD is inherited, but non-genetic factors are also effective.[5]

In addition to prenatal and perinatal (late pregnancy and delivery) factors, maternal (maternal) diet and lifestyle are also risk factors. Factors such as advanced maternal age, maternal metabolic conditions during pregnancy, medication use, weight gain and hypertension, and specific factors such as bacterial or viral infections experienced by the mother have been associated with ASD risk and developmental delay.

While genetic and non-genetic factors are effective in ASD, only one factor does not constitute ASD. These factors come together and cause the development of ASD.[5]

It has been reported that ASD affects 1% to 2% of the world population and occurs in one in 54 children. Diagnosis is four times more common in boys than girls.[6]

Although it is never too late for ASD treatment, it should be started as early as possible in order to get maximum efficiency from the treatment. The ideal time is before the age of two when neuroplasticity and brain growth develop rapidly.[7]

AUTISM AND THE IMMUNE SYSTEM

The first recommendation for a link between the immune system and ASD was made in children with ASD because of undetected rubella antibodies after rubella vaccination.[8] Since then, the immune system and abnormal immune function; There has been evidence of a significant effect on ASD, including inflammation, cytokine dysregulation and anti-brain autoantibodies. This evidence has enabled researchers to investigate the potential role of immune dysregulation and autoimmunity in ASD more closely.[9]

Some studies in animal models have confirmed that an immune challenge during pregnancy results in behavioral abnormalities in the fetus.[8] There are several ways the gestational environment can affect neurodevelopment in the child. Besides active infection, the mother's immune response to infection can also be prenatal risk factors.[9] In a study conducted through animal models, Shi et al.[10] Proved that an immune response activated in the mother alone, without any infection, is sufficient to induce changes in the offspring. Infections such as rubella or influenza virus during pregnancy can create an inflammatory immune environment and stimulate the production of maternal cytokines that can not only directly affect the placenta, but also cross the placenta and enter the fetal compartment,

thereby having lasting effects on the development of the fetus. These effects can also occur in the absence of active infection, although there is an inflammatory response or immune regulatory disorder. Also, in some women, anti-brain autoantibodies may similarly be produced that can gain access to the developing fetal brain and bind to fetal proteins and thus alter the course of neurodevelopment.[9] The presence of maternal anti-fetal brain autoantibodies has also been reported to play a role in ASD. Monkeys prenatally exposed to human immunoglobulin G (IgG) produced from mothers of children with ASD have been shown to exhibit hyperactivity or impaired social behavior.[8]

Maternal immune activation (MIA) occurs with inflammation. This inflammatory state causes an increase in interferon-gamma (IFN-γ) and IL-17A cytokines secreted by CD4 + T cells and a systemic deficiency in regulatory T cells / Treg.[8]

In order to model MIA as a risk factor in ASD, direct infection or lipopolysaccharide (LPS) was used to mimic infection in pregnant mice. With these various approaches, inflammation is triggered in the mother. Simulating MIA in this way resulted in offspring displaying an ASD-like phenotype.[10] Therefore, activation of the maternal immune system during fetal development is an important factor in ASD etiology and may lead to changes in neurodevelopment.[9]

INTERLEUKIN-17A IN AUTISM

IL-17A is a cytokine that can cause inflammatory diseases by generating various autoimmune responses. Autoimmunity in brain tissue plays a pathogenic role in autism. Immune system abnormalities have been commonly observed in and around the brain of individuals with ASD. Studies have found chronic neuroinflammation in ASD, indicated by increased activation of microglia and astrocytes and the production of cytokines and chemokines in the brain.[11]

A cross-sectional study was conducted on 45 children with ASD aged 6-11 years by Al-Ayadhi and Mostafa. In this study, it was shown that there is a positive correlation between IL-17A and ASD severity. High serum IL-17A levels were seen in approximately 50% of children with autism (67.9% of children with severe symptoms and 17% of children with mild to moderate ASD).[12]

It is known that MIA affects fetal brain development and causes symptoms of autism spectrum disorder. IL-17A is also a mediator responsible for the pathogenesis of MIA-induced ASD. Injection of recombinant IL-17A into the fetal brain ventricles resulted in ASD-like behavioral and histopathological abnormalities.[13]

The task of IL-17A in immunity is to provide a protective effect. The infection causes the production and secretion of interleukin-6 (IL-6), a cytokine. In the presence of cytokine transforming growth factor β (TGFβ /transforming growth factor beta), IL-6 stimulates differentiation of undifferentiated CD4 + T cells into Th17 cells. The transcription factor t (RORγt) (Retinoic acid receptor-related orphan receptor gamma-t) supports the transcription of IL-17A. IL-17A signaling plays a protective role in adaptive immunity. The dysregulation of Th17 cells and high levels of IL-17A production is associated with autoimmune diseases and inflammatory disorders.[11]

The role of IL-17A in ASD; As a result of its inappropriate activity, it may cause ASD formation prenatally by affecting the brain development of the fetus. In the case of MIA, IL-6 is induced and stimulates the differentiation of Th17 cells in the mother. This causes an increase in IL-17A secretion. IL-17A then crosses the placental barrier where it can act on cells expressing the IL-17RA receptor in the developing nervous system. Consequently, IL-17A can alter a variety of developmental processes, including neuronal connectivity. In these ways, inappropriate Th17 cell and IL-17A activity may adversely affect prenatal development.[11]

AUTISM AND BRAIN

In individuals with ASD, many brain structures and systems have been studied and found to be abnormal in structure or function compared to typically developing individuals. These studies include many structures of the brain. Studies have shown that certain behavioral disorders can be associated with dysfunctions in certain brain regions or modules.[14] Maternal Th17 cells create cortical and behavioral abnormalities in children affected by MIA. One of the brain regions where these cortical abnormalities are localized is a region that covers the S1DZ of the primary somatosensory cortex.[15] The primary somatosensory cortex is located in the parietal lobe and is responsible for processing the somatic senses. These senses are perceived thanks to receptors located throughout the body that detect touch, the body's position in space, pain and temperature. When one of these senses is perceived, the information is sent to the thalamus and then to

the primary somatosensory cortex and processed there.[16] The cortical phenotype is characterized by the increase in the number of Fos + activated neurons in S1DZ. Fos is a transcription factor strongly induced by neural activity. It is induced in many brain regions in response to a wide variety of external stimuli. Emotional signals also trigger gene induction and increase.[17]

Structural and functional changes in the somatosensory cortex were found in studies conducted in individuals suffering from mental disorders related to abnormal emotional regulation such as bipolar disorder, schizophrenia, and anxiety disorders. Common observations in the somatosensory cortex of individuals with mood disorders include changes in gray matter volume, cortical thickness, abnormal functional connectivity with other brain regions, and changes in metabolic rates.[18]

The decrease in neural activity in S1DZ has been shown to be effective in recovering behavioral abnormalities in offspring who were prenatally exposed to maternal inflammation.[15]

Another system in the brain associated with ASD symptoms; is a neuromodulatory system called locus coeruleus/norepinephrine (LC/NE). Theories of LC/NE and its functioning have been developed over the last few years. These neuromodulatory systems, derived from the brainstem and midbrain nuclei, are linked to all areas of the brain. The ever-changing environment that individuals have to adapt to requires tremendous flexibility to adapt it, and neuromodulation is the mechanism by which the central nervous system obtains maximum flexibility.[14]

The midbrain-located LC mediates attention to function and is the main center of the locus coeruleus-norepinephrine system.[19] LC, the largest NE core in the brain; regulates the processing of sensory information, motor behavior, arousal and cognitive processes and reflects them to the entire central nervous system. It seems very likely that the disorders in the LC/NE system are related to the abnormal regulation of emotions in ASD. In a mouse model, it was found to cause persistent changes in adult emotional behavior and changes in LC neuron activity by inhibiting NE signaling during development.[14]

MECHANISM OF FEVER

Fever occurs in response to the entry of pathogenic microorganisms into the body, and cytokines also mediate fever. The fact that fire has been preserved throughout evolution strongly maintains that fiery temperatures provide a survival advantage. In fact, fever is a protective mechanism that prevents attacks by invading pathogens. Fever temperatures reduce the efficacy and infectious potential of pathogens. Induction and maintenance of fever during infection occurs through tightly coordinated interaction between the innate immune system and the neuronal circuitry in the central and peripheral nervous systems. The immune system's detection of infection begins with the attachment of pathogen-related molecular models to pathogen recognition receptors.[20] When any microbe enters our body, it is detected by these receptors and ingested by immune system cells called macrophages. Macrophages stimulate other immune system cells to produce a pyrogenic substance called interleukin-1 (IL-1). IL-1 or other pyrogens (fire makers) are secreted into the blood and travel to the fever center in the hypothalamus. When the hypothalamus comes into contact with IL-1 and other pyrogens, it realizes that 37°C is not enough and produces a chemical called prostaglandin E2 (PGE2). PGE2 raises the firing threshold above 37°C.[21] PGE2 is an endogenous lipid molecule that regulates important physiological functions including calcium signaling, neuronal plasticity, and immune responses. Exogenous factors such as diet, exposure to immunological agents, toxic chemicals and drugs may affect PGE2 levels in the brain during development, and therefore PGE2 is also thought to have a potential effect on autism disorders.[22]

AUTISM AND FEVER

Children with ASD have improved behavioral symptoms during fever.[23] Some children with ASD exhibit improved behavior and improved social communication during periods of fever.[24] There are theories that fever may affect brain function at the cellular level by affecting the production of immune system signaling proteins known as cytokines.[23] It has been found that social behavioral deficiencies in children exposed to MIA can be temporarily rescued by the inflammatory response induced by lipopolysaccharide (LPS) administration. In this behavioral recovery, a decrease in neuronal activity in the S1DZ, which is responsible for behavioral phenotypes associated with children previously exposed to MIA, was observed.[16] Fever is an expression of inflammation, so one study measured inflammatory molecule levels before and after injection in four groups of mice. MIA mice

showed a sharp increase in IL-17A not seen in control mice. Researchers have suggested that exposure to maternal inflammation in the uterus leads to persistent changes in the immune system, which may cause MIA mice to release IL-17A in response to other immune triggers.[25]

IL-17A receptors (IL-17Ra) are found throughout the cortex of a mouse. In a study based on this, researchers found that injecting IL-17A into the somatosensory cortex of MIA mice decreased the number of Fos + activated neurons in the S1DZ region, calming their neural activity and increasing their sociability.[24] To confirm the importance of IL-17A in fever, the researchers inhibited IL-17A or disabled IL-17A receptors. But despite this, the symptoms of autism did not go away. They also showed that raising the mice's body temperature also did not affect behavior. Namely, IL-17A was determined to be absolutely necessary for the reversal of ASD symptoms.[26] Also; During fever, behavioral state changes in autism are assumed to be due to the temporary normalization of key components in a functionally impaired LC/NE system. Fever temporarily corrects the regulatory functions of the LC/NE system and thus improves ASD behavior.[24] Strategies aimed at normalizing the neuromodulatory functions of the LC/NE system are seen as a promising target for the effective treatment of ASD.[14]

Conclusion

Cytokines such as IL-17A, which are released as a result of any immune response in the mother during pregnancy, affect the brain development of the baby by crossing the placenta and causing ASD.

ASD has been associated with some abnormal conditions in the S1DZ region of the brain and the LC/NE system. When these conditions in the brain were examined, it was seen that there were some changes during fever. In the S1DZ region, as neuron activity decreases during fever, the overreaction situation seen in autism is suppressed.

In the neuromodulator system called LC/NE, it was observed that the abnormal function observed in individuals with autism was temporarily normalized during fever. Thus, it was determined that by cytokines such as IL-17A released during fever, abnormal functions in the brain were normalized and symptoms disappeared during this time. Interestingly, a cytokine called IL-17A has two opposite functions. While it causes the developmental disorder of the fetus in the mother's womb, the same cytokine repairs this disorder during inflammation, namely fever, in the future of the individual. In this case, it is understood that our immune system plays a vital role in our development and behavior from the fetus and how complex a system it is. The mechanism of immune responses and IL-17 in our body is still not fully resolved. If these mechanisms can be solved in detail, it is thought that cytokines can be used for the definitive treatment of ASD.

It may be promising to mimic the fever state by administering IL-17A as a therapy to people with ASD or by activating IL-17A receptors. In addition, strategies aimed at stopping the activity of neurons in the somatosensory cortex or normalizing the neuromodulatory functions of the LC/NE system can be used for treatment. However, due to the many different and opposite functions of IL-17A, more research is needed to understand whether it will have side effects.

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REFERENCES

1. Ramani T, Auletta CS, Weinstock D, Mounho-Zamora B, Ryan PC, Salcedo TW, et al. Cytokines: The good, the bad, and the deadly. Int J Toxicol 2015;34:355-65.
2. Gu C, Wu L, Li X. IL-17 family: Cytokines, receptors and signaling. Cytokine 2013;64:477-85.
3. Ma WT, Yao XT, Peng Q, Chen DK. The protective and pathogenic roles of IL-17 in viral infections: Friend or foe? Open Biol 2019;9:190109.
4. Iwakura Y, Nakae S, Saijo S, Ishigame H. The roles of IL-17A in inflammatory immune responses and host defense against pathogens. Immunol Rev 2008;226:57-79.
5. Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. Lancet 2018;392:508-20.
6. Ung D, Wood JJ, Ehrenreich-May J, Arnold EB, Fuji C, Renno P, et al. Clinical characteristics of high-functioning youth with autism spectrum disorder and anxiety. Neuropsychiatry (London) 2013;3:10.2217/npy.13.9.
7. Dunlap JJ, Filipek PA. CE: Autism Spectrum Disorder: The Nurse's Role. Am J Nurs 2020;120:40-9.
8. Gładysz D, Krzywdzińska A, Hozyasz KK. Immune abnormalities in autism spectrum disorder-could they hold promise for causative treatment? Mol Neurobiol 2018;55:6387-35.
9. Meltzer A, Van de Water J. The role of the immune system in autism spectrum disorder. Neuropsychopharmacology 2017;42:284-98.

10. Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. J Neurosci 2003;23:297-302.
11. Wong H, Hoeffer C. Maternal IL-17A in autism. Exp Neurol 2018;299:228-40.
12. Al-Ayadhi LY, Mostafa GA. Elevated serum levels of interleukin-17A in children with autism. J Neuroinflammation 2012;9:158.
13. Sasaki T, Tome S, Takei Y. Intraventricular IL-17A administration activates microglia and alters their localization in the mouse embryo cerebral cortex. Mol Brain 2020;13:93.
14. London EB. Neuromodulation and a reconceptualization of autism spectrum disorders: Using the locus coeruleus functioning as an exemplar. Front Neurol 2018;9:1120.
15. Shin Yim Y, Park A, Berrios J, Lafourcade M, Pascual LM, Soares N, et al. Reversing behavioural abnormalities in mice exposed to maternal inflammation. Nature 2017;549:482-7.
16. Webb WG. Organization of the Nervous System I. In: Webb WG, editor. Neurology for the Speech-Language Pathologist. 6th ed. St. Louis: Mosby; 2017. p. 13-43.
17. Cho JH, Rendall SD, Gray JM. Brain-wide maps of Fos expression during fear learning and recall. Learn Mem 2017;24:169-81.
18. Kropf E, Syan SK, Minuzzi L, Frey BN. From anatomy to function: The role of the somatosensory cortex in emotional regulation. Braz J Psychiatry 2019;41:261-9.
19. Bast N, Poustka L, Freitag CM. The locus coeruleus-norepinephrine system as pacemaker of attention - a developmental mechanism of derailed attentional function in autism spectrum disorder. Eur J Neurosci 2018;47:115-25.
20. Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: The immune system feels the heat. Nat Rev Immunol 2015;15:335-49.
21. Blatteis CM, Sehic E. Cytokines and fever. Ann N Y Acad Sci 1998;840:608-18.
22. Wong CT, Ussyshkin N, Ahmad E, Rai-Bhogal R, Li H, Crawford DA. Prostaglandin E2 promotes neural proliferation and differentiation and regulates Wnt target gene expression. J Neurosci Res 2016;94:759-75.
23. Curran LK, Newschaffer CJ, Lee LC, Crawford SO, Johnston MV, Zimmerman AW. Behaviors associated with fever in children with autism spectrum disorders. Pediatrics 2007;120:e1386-92.
24. Mehler MF, Purpura DP. Autism, fever, epigenetics and the locus coeruleus. Brain Res Rev 2009;59:388-92.
25. Reed MD, Yim YS, Wimmer RD, Kim H, Ryu C, Welch GM, et al. IL-17a promotes sociability in mouse models of neurodevelopmental disorders. Nature 2020;577:249-53.
26. Hoogenraad CC, Riol-Blanco L. Interleukin-17: A social cytokine. Cell 2020;181:517-9.