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Relationship between Attention Deficit Hyperactivity Disorder and Prenatal Inflammation

Prenatal Enflamasyon ve Dikkat Eksikliği Hiperaktivite Bozukluğu İlişkisi

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is a chronic neurodevelopmental disorder characterized by attention deficit, hyperactivity, and impulsivity. ADHD presents impairments in academic, social, emotional and cognitive domains. Genetic and environmental factors play a role in the etiology of ADHD. Numerous studies showed that parameters associated with inflammation were higher in patients with ADHD. Due to the co-occurence of ADHD and allergic and immunologic disorders, it is thought that the immune system has an effect on ADHD etiology. Previous studies showed that there is a strong association between prenatal inflammation exposure and neurodevelopmental disorders. Maternal diabetes mellitus, body mass index, preeclampsia, infections and chronic or autoimmune disorders of the mother are accepted as prenatal risk factors of ADHD. All these risk factors are associated with the immune profile of the mother. Because of this, the association between ADHD and intrauterine inflammation exposure is attractive. In this paper, the association of ADHD and perinatal inflammation due to maternal immune activation is reviewed.

Keywords: Inflammation, attention deficit hyperactivity disorder, immune activation

Öz

Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) dikkat eksikliği, hiperaktivite ve dürtüsellik ile karakterize kronik, nörogelişimsel bir bozukluktur. Akademik, sosyal, duygusal ve bilişsel alanlarda bozulma ile seyreder. DEHB etiyolojisinde genetik ve çevresel birçok faktör rol oynamaktadır. DEHB tanısı alanlarda yapılan çok sayıda çalışmada enflamasyon ile ilişkili parametrelerde yükseklik saptanmıştır. Alerjik ve immünolojik durumlar ile DEHB birlikteliği, DEHB etiyolojisinde immün sistem etkisini düşündürmektedir. Prenatal dönemde maruz kalınan enflamasyon ile nörogelişimsel bozukluklar arasındaki güçlü bir ilişki olduğu gösterilmiştir. DEHB oluşumuna neden olabilecek prenatal risk faktörlerinden kabul edilen maternal diyabet, vücut kitle indeksi, preeklampsi, enfeksiyon, annenin kronik veya otoimmün hastalıkları gibi parametreler annenin enflamatuvar profili ile ilişkili bulunmaktadır. Bu nedenle intrauterin enflamasyona maruziyet ile DEHB arasındaki ilişki ilgi çekmektedir. Bu derlemede, maternal immün sistem hiperaktivasyonuna neden olabilecek durumlar ile olası prenatal nöroenflamasyon ve DEHB ilişkisi gözden geçirilmiştir.

Anahtar sözcükler: Enflamasyon, dikkat eksikliği hiperaktivite bozukluğu, immün aktivasyon

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ATTENTION Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that affects approximately 5-10% of children worldwide and is characterized by attention deficit, hyperactivity and impulsivity (American Psychiatric Association 2013). ADHD results in impairment of academic, social, emotional and cognitive areas. It is more frequent in boys than in girls. Although it is mostly known as childhood disorder, it is observed that approximately 50% of those diagnosed with ADHD continue to have complaints in adulthood (Faraone et al. 2015).

The etiology of ADHD is multifactorial, complicated and still being studied. Although the effect of genetic predisposition (75%) is certainly accepted (Bierderman and Faraone 2005), it is also clear that heredity is not the only cause. It is thought that 20%-30% of the parameters associated with ADHD are environmental factors (Verlaet et al. 2014). Among the environmental factors, one of the most interesting and researched topics is the factors that affect brain development in the prenatal period. It is suggested that there is a strong relationship between neurodevelopmental disorders and early life exposure to inflammation (Oldenburg et al. 2020).

Inflammation occurs in the brain as a result of activation of glial cells, cytokines, chemokines, prostaglandins, nitric oxide (NO), reactive oxygen radicals, and the infiltration of immune system cells (Alvarez-Arellano et al. 2020). The role of neuroinflammation in ADHD pathophysiology is increasingly researched. In the literature, there are studies showing that serum cytokine levels are higher in the group with ADHD symptoms compared to the group not diagnosed with ADHD (Donfrancesco et al. 2016, Anand et al. 2017, Darwish et al. 2018). In a small sample study, it is shown that the polymorphism in the interleukin 1-receptor antagonist (IL-1Ra) gene is associated with ADHD (Segman et al. 2002). Oades et al. (2010) reported that there is a relationship between proinflammatory serum cytokines and ADHD symptom severity. Levels of anti-basal ganglia antibody (Toto et al. 2015) and antibody against the dopamine transporter (Giana et al. 2015, Adriani et al. 2018), which should be considered as markers of inflammation, were found to be high in those diagnosed with ADHD. In the only study performed on cerebrospinal fluid (CSF), it is reported that TNF-beta levels are higher and IL-4 levels are lower in CSF of ADHD patients (Mittleman et al. 1997). Two interesting studies showed that the neutrophil/lymphocyte ratio is high in children with ADHD and can be interpreted in favor of inflammation (Avcil 2018, Önder et al. 2021). All these studies have small samples and are heterogeneous in terms of the molecule investigated. Therefore, it is difficult to make comparison between studies.

On the other hand, the connection between ADHD and immunological diseases/allergy of both patient and mother has been investigated. While the comorbidity of ADHD is 30-50% higher in the atopic diseases (Schans et al. 2017), the relationship between juvenile arthritis, Type 1 diabetes, autoimmune thyroiditis (Nielsen et al. 2017), psoriasis, Crohn's and ulcerative colitis (Hegvik et al. 2019) and ADHD increases the interest in the immune system.

Maternal risk factors such as obesity, inflammatory and immune system diseases are associated with the inflammatory profile of the mother. Thus, it is strengthening the potential

role of inflammation exposed during neural development in ADHD pathophysiology (Terasaki and Schwarz 2016, Dunn et al. 2019). In this paper, maternal immune system hyperactivation and the relation between possible perinatal neuroinflammation and ADHD will be reviewed.

Maternal diabetes mellitus and adiposity

It is reported that high blood glucose in pregnancy due to maternal diabetes creates an inflammatory environment by causing oxidative stress through free radicals (Ornoy et al. 2015). As a result of this fetal brain can be affected, behavioral and neurodevelopmental consequences can occur (Eidelman and Samueloff 2002, Chandna et al. 2015). In animal studies, it is shown that gestational DM (GDM) and the infection on it affect the pathways associated with psychiatric disorders by causing transcriptional changes (Money et al. 2018). In a study using Swedish national registry data, it is observed that the presence of maternal Type 1 DM increases the risk of offspring ADHD by 35%, while the addition of socioeconomic parameters does not make a difference (Ji et al. 2018). In a population-based case-control study, it is observed that the presence of maternal Type 1DM increases the risk of offspring ADHD (OR =1.6), while a significant relationship is not shown with the presence of Type 2DM (Instanes et al. 2017). In another study, no relationship is found between adolescent ADHD and maternal Type 1 DM, but in this study the attention-related problem may not have been reflected in the test performed to measure due to those receiving ADHD treatment (Bytoft et al. 2017). In the study of Nomura et al. (2012) (n=212), it is reported that the association of GDM and low socioeconomic level increases the risk of offspring ADHD. The study of Li et al. (2014) showed that GDM or pregestational DM in normal-weight or obese mothers have no effect on the risk of offspring ADHD. Kong et al. (2018) reported that the presence of severe obesity together with pregestational DM in the mother increases the risk of offspring ADHD six times, but the effect of GDM is not clear.

In another study, it is shown that the presence of maternal Type 1 (57%) and Type 2 DM (43%) increases the risk of offspring ADHD, the presence of GDM does not increase, but when analyzed the subgroups according to whether requiring antidiabetic treatment, the risk increases by 26% in the presence of GDM requiring treatment (Xiang et al. 2018). In conclusion, it is thought that the presence of maternal DM can be related to the risk of offspring ADHD and can be affected by factors such as socioeconomic level, body mass index, DM type, and whether or not requiring treatment.

It is known that leptin is an inflammatory hormone that is released in proportion to the amount of adipose tissue. It is thought that pre-pregnancy body mass index (BMI) of mother can be associated with the risk of offspring ADHD, and inflammation can play a role in this effect. A meta-analysis showed that maternal overweight (30%) and obesity (42%) before pregnancy increase the offspring ADHD risk (Jenabi et al. 2019). This meta-analysis includes observational studies conducted in America and European countries, and in some studies BMI was recorded based on self-report. Similarly, an older meta-analysis found that maternal overweight or obesity before pregnancy was associated with offspring

ADHD (Sanchez et al. 2018). However, this meta-analysis was conducted on a limited database with 6 studies.

Preeclampsia

In animal studies, it is shown that interleukin-17a (IL-17a) activation in the fetal brain occurs in response to maternal immune activation, which can lead to behavioral disorders of offspring (Choi et al. 2016). Based on the studies showing that IL-17a and other cytokines increase in preeclampsia, it is suggested that maternal inflammation plays a role in preeclampsia (Böhm et al. 2019). Evidence on the relationship between preeclampsia and ADHD in human studies is conflicting. In addition to studies showing that preeclampsia increases the risk (Golmirzaei et al. 2013, Böhm et al. 2019), there are also publications showing that the risk does not increase (Gustafsson and Kallen 2011, Amiri et al. 2012). Most of these studies have small sample and/or are case-control studies, and one of the limitations of studies is the other ADHD risk factors (such as premature birth, low birth weight) have not been excluded. In a systematic review, it is reported that preeclampsia increases the risk of offspring ADHD by 30% (Maher et al. 2019). In a prospective cohort study, it is reported that preeclampsia increases the risk of diagnosing ADHD at the age of 7 by 3 times and by 4 times at the age of 10 (Dachew et al. 2019). A new cohort study shows that preeclampsia increases the risk of offspring ADHD by 15%, and when low birth weight is added to preeclampsia, this rate increases to 43% (Maher et al. 2020).

Maternal other chronic disorders and infection

In the first prospective human study investigating maternal inflammation and the risk of offspring ADHD, maternal cytokine levels during pregnancy (IL-6, TNF-alpha, Monocyte chemoattractant protein-1) are examined (Gustfasson et al. 2020). A relationship is found between cytokine levels in the third trimester of pregnancy and the increase in ADHD symptoms at 4-6 years old. The pathway of maternal inflammation in the offspring ADHD risk can be explained by the following mechanisms; maternal cytokines a) can cross the placenta and cause an increase in cytokines in the fetal brain, b) can increase placental cytokine expression by causing epigenetic changes in the placenta, c) can stimulate immune cells in the decidua, which can increase cytokine release at the maternal-fetal interface, and d) increased intrauterine cytokines can trigger fetal inflammatory response and can contribute to the formation of inflammation in the fetal brain (Gustfasson et al. 2020).

In the literature, there are studies investigating immunological diseases in the mother and the risk of offspring ADHD. It is shown that asthma and other atopic diseases are associated with the proinflammatory process and can trigger the inflammatory response in the placenta and cause microglia activation in the fetal central nervous system (Cowell et al. 2019). Instanes et al. (2017) reported that maternal multiple sclerosis (80%), rheumatoid arthritis (70%), hypothyroidism and asthma (50%) increase the risk of offspring ADHD. In a population-based cohort study investigating the risk of offspring ADHD associated with asthma in the mother and father, it is found that asthma in mother (HR =1.41, 95%

Cl =1.36-1.46) or in father (HR =1.13, 95% Cl =1.08-1.18) or in both of them (HR =1.56, 95% Cl =1.39-1.76) increases the risk of offspring ADHD. In addition, the risk of ADHD (HR =1.25, 95% Cl =1.08-1.44) is found to be higher in the group who had a maternal asthma exacerbation during pregnancy compared to did not experience an exacerbation group (HR =1.12, 95% Cl =1.00-1.25) (Liu et al. 2019).

It is reported that maternal infections requiring hospitalization during pregnancy (Ginsberg et al. 2019), urinary system infections (Dreier et al. 2016) and the presence of fever especially in the first trimester (Gustavson et al. 2019) increase the risk of ADHD. In case of infection and fever, it is assumed that the type of infectious agent is not important, resultant immune activation is associated with the risk of ADHD. However, there are studies in the literature that do not find a significant relationship between the risk of offspring ADHD and high maternal C-reactive protein (CRP), which is considered as an inflammation marker (Werenberg et al. 2016, Ginsberg et al. 2019, Chudal et al. 2020, Jallow et al. 2020).

Prenatal smoking and alcohol exposure

The negative effects on the fetus of alcohol and tobacco usage during pregnancy are well known. Maternal smoking during pregnancy can lead to many negative consequences such as premature birth, low birth weight, placental detachment, impaired fetal lung development, susceptibility to infection, and sudden infant death (Pineles et al. 2014). Two recent meta-analysis showed that maternal smoking during pregnancy increases the risk of offspring ADHD (OR =1.775, 95% CI =1.324-2.379, OR =1.60 95% Cl =1.45-1.76, respectively) (Dong et al. 2018, Huang et al. 2018). On the other hand, in sibling studies, no significant relation is found between smoking during pregnancy and ADHD risk (OR =1.04, 95% Cl =0.95-1.15) (Huang et al. 2018). In these studies, the data of smoking during pregnancy is based on the self-report. As shown in previous studies, mothers tend to report their smoking at a lower rate (Dietz et al. 2011, Tong et al. 2015), thus the self-reported smoking data is limitation of these studies. In addition, many confounding factors (such as the order of pregnancy, the difference in smoking attitude between pregnancies, the father's smoking, socioeconomic level, parental ADHD) can affect the results in these studies.

Nicotine is metabolized to cotinine in the liver. The relationship is not found between the maternal cotinine level and offspring ADHD in two studies using parental report scales (Eskenazi and Trupin 1995, Dürr et al. 2015). It is reported that prenatal exposure to nicotine increases the risk of ADHD in a dose-dependent manner (Sourander et al.2019). In this study, cotinine levels were divided into 3 groups as heavy (>50 ng/mL), medium (20-50 ng/mL) and none or low (<20 ng/mL). There was a significant relationship between heavy cotinine level and ADHD both in uncorrected analysis (OR =2.95, 95% Cl =2.25-3.88) and in corrected analysis by adding the parameters of maternal age, socioeconomic level, psychopathology and substance use, father's age-psychopathology, birth weight of child (OR =2.21, 95% CI =1.63-2.99).

Nicotine, an acetylcholine agonist, is thought to affect the fetal central nervous system development and dopaminergic system by crossing the placenta (Dwyer et al. 2009). There is increased evidence that smoking during pregnancy causes changes in DNA methylation and micro-RNA expression via gene-environment interactions (Knopik et al. 2012, Rzehak et al. 2016). There are many toxins in cigarettes that play immunomodulatory role. These toxins can cause inflammation by increasing mediators such as IL-8 and TNF-alpha (Chung 2005, Chahal et al. 2017). The association of smoking with autoimmunity and inflammation is shown in many studies (Lee et al. 2012). In conclusion, recent studies showed that the relationship between smoking during pregnancy and ADHD is thought to be caused by genetic, epigenetic and environmental factors rather than direct intrauterine effects.

The teratogenic effects of prenatal high-dose alcohol exposure are well known. However, cognitive and behavioral effects in offspring were the subject of many studies. It is shown that there is a strong relationship between binge drinking and/or exposure to prenatal high-dose alcohol (4 drinks or approximately 56 g of pure alcohol) and ADHD symptoms in offspring (Yolton et al. 2014, Popova et al. 2016). It is thought that alcohol passes through the placenta and increases the production of cytokines and chemokines by activating the maternal immune system, especially in the case of medium-high dose alcohol exposure during early pregnancy (Terasaki et al. 2016). The results regarding the effects of low-moderate alcohol intake during pregnancy on the fetus and its relationship with ADHD are inconsistent (San Martin Porter et al. 2019).

In addition to studies showed that episodic use of at least 4 drinks or regular low-medium dose alcohol use during pregnancy increases the risk of offspring ADHD (Kelly et al. 2009, Sayal et al. 2013, Pagnin et al. 2019), there are publications reported that low-moderate alcohol use is not associated with offspring ADHD (Kelly et al. 2012, Niclasen et al. 2014, San Martin Porter et al. 2019). In these studies, alcohol use, amount and frequency are evaluated based on the maternal self- report. This may lead to report lower levels due to social reasons. However, discrepancies in other factors such as socioeconomic level and genetic predisposition could affect the results of the study.

Maternal stress

Many studies showed that psychological stress impairs immune system functions in healthy, non-pregnant adults. Stressful life events, chronic and acute stress, traumatic stress and negative childhood experiences are the types of stress. The relationship between stress and inflammation is dependent on the weak regulation of the hypothalamus-pituitary-adrenal axis (HPA) on the immune system. Due to stress, increased cortisol and proinflammatory cytokines affect the relationship between glucocorticoid and immune system (Hantsoo et al. 2019).

In the literature, there are publications showing that maternal stress during pregnancy increases the risk of offspring ADHD (Li et al. 2010, Class et al. 2014, Say et al. 2016, MacKinnon et al. 2018, Okano et al. 2019). However, as well as maternal stress, other maternal factors such as the socioeconomic level, coping skills, mental illness and the

presence/absence of social support may also contribute to this risk. Additionally, it is not clear that exposure to stress on which period of pregnancy is more determinant. Only Li et al. (2010) reported that maternal exposure to bereavement in the third trimester may be associated with an increased risk of offspring ADHD (OR =1.67, 95% Cl =1.09-2.56). It is reported that exposure to stress during pregnancy results in fluctuations in placental inflammatory cytokines (placental CRP) and increased risk of offspring ADHD in boys (OR =3.37, 95% Cl =1.78-6.38), not in girls (OR =1.02, 95% CI =0.44-2.38) (Shao et al. 2020). The relationship between ADHD risk and exposure to stress, resulting inflammatory response may vary depending on gender.

Air pollution

Air pollution contains many elements; particulate matter, gases (nitrogen oxide), trace metals (lead, manganese, arsenic) and mainly human origin, absorbed organic contents (such as burning fossil fuel). Traffic-related air pollution is one of the biggest contributors to global air pollution and poses a serious health problem, especially in cities with high traffic (Myhre et al. 2018). Exposure to city air containing particulate matter can lead to asthma, lung cancer, fibrosis, cardiovascular diseases, as well as many diseases such as dementia, depression, and schizophrenia (Anderson et al. 2012, Newby et al. 2015, Myhre et al. 2018). The developing brain is more susceptible to toxic exposures. The blood-brain barrier in the fetus is immature and the fetus's ability to detoxify and eliminate is limited (Ek et al. 2012).

Polycyclic aromatic hydrocarbons (PAH) and trace metals (the components of air pollution) can pass through the placenta (Zhang et al. 2017). In some studies, it is shown that prenatal PAH exposure due to air pollution is associated with low intelligence level, ADHD, attention and behavioral problems (Perera et al. 2014, Peterson et al. 2015). It is reported that the risk increases when socioeconomic difficulties, difficult life events, and lack of care and nutrition are added to prenatal PAH exposure (Perera et al. 2018, Pagliaccio et al. 2020). However, there are studies reporting that there is no relationship between air pollution and ADHD (Forns et al. 2018a, Forns et al. 2018b, Oudin et al. 2019, Skogheim et al. 2020). In these studies, differences in diagnostics, biased sample selection, heterogeneous group, and limitations on the measurement of air pollution exposure are noted.

Although the effects of air pollution components on the central nervous system are not fully understood, inflammation is thought to play a role. Both cohort and postmortem studies showed an increase in neuroinflammatory markers in the brain of children and adults exposed to air pollution (Calderón-Garcidueñas et al. 2008, Calderón-Garcidueñas et al 2011, Calderón-Garcidueñas et al. 2012).

Animal studies of maternal immune activation

In animal studies, maternal immunity is activated to investigate the relationship between neuroinflammation and ADHD. In these studies, changes in the brain structure were observed as a result of exposure to prenatal inflammation. Volume loss of the cortical gray matter, the prefrontal cortex and the anterior cingulate cortex, which are brain regions

associated with ADHD, are shown. In addition, changes in dopaminergic, serotonergic, glutaminergic, and GABAergic systems associated with ADHD are detected (Dunn et al. 2011).

Conclusion

Prenatal causes of ADHD have been the subject of research for many years. The relationship between ADHD and exposure to prenatal inflammation, neuroinflammation arouse interest in recent years. There is no strong evidence of peripheral inflammation and neuroinflammation, since there are no postmortem ADHD studies in the literature. Increasing evidence points to the importance of prenatal inflammation and immune response in ADHD pathophysiology. However, further studies with large samples and methodologically strong are needed. Identification of the etiology and pathophysiology of ADHD will allow effective prevention strategies to be developed.

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