Chapter 2

The Role of Environmental Factors in Etiology of Attention-Deficit Hyperactivity Disorder

Esra Guney, Fatih Hilmi Cetin and Elvan Iseri

Additional information is available at the end of the chapter

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Abstract

Environmental factors in etiology of ADHD Attention deficit and hyperactivity disorder (ADHD) is one of the most common developmental disorders of childhood. It was reported that it is a disease that affects 5.29% of children and adolescents in the entire world. Although ADHD is a disorder with high inheritability, genetic factors are not the only explanation to ADHD etiology. ADHD is a disorder etiology which has genetic and environmental components and gene-environment interaction. In spite of the fact that many environmental factors are linked to ADHD, the number of environmental factors that are proven to be in significant cause-effect relation is too small. In other words, in presence of proper genetic basis, disease appears in presence of many environmental factors each of which have a slight effect, its severity or prognosis is variable. Environmental factors that are most commonly linked to ADHD pathophysiology are; complications during pregnancy, natal and postnatal period, several toxins and food substances. It has been considered that exposure to risk factors that may affect development of the brain in any of these periods will have long-term effects on behavior. Along with mother's cigarette or alcohol use during pregnancy, emotional difficulties, medical diseases and complications of pregnancy; natal complications, low birth weight, premature birth, post mature birth, physical traumas that may affect brain development in early childhood, psychosocial difficulties are also found to be related to ADHD. Studies of gene-environment interaction also note the importance of environmental factors. For example, a study showed that in cases which carry 7 repeated alleles of DRD4, exposure to prenatal cigarettes causes more severe symptoms of ADHD. The purpose of this paper is to evaluate the role of

environmental factors in etiology of ADHD, review these factors in the light of related literature and, lastly, to mention gene-environment interaction.

Keywords: ADHD, risk factors, enviromental factors, etiology

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a disorder with strong genetic origins, and a number of factors play a role in its etiology [1]. Although ADHD is characterized by the symptoms of attention deficit, hyperactivity, and impulsivity, it was reported that it might have a phenotypic etiological heterogeneity, and all those variables might affect the outcomes of the disorder [2].

The studies on the etiology of ADHD have focused on genetic, neurochemical, and brain imaging methods, as well as the environmental risk factors. Similar to many psychiatric disorders, it appears that interactions of the small effects of a number of genes with each other and the environment result in the development of the disorder [1-3]. Determining the environmental risk factors that play a role in the etiology of the disorder or affect the outcomes negatively is important to provide more comprehensive interventions starting from early developmental periods, and to take required precautions in those patients [4]. It has been currently shown that various environmental risk factors probably increase the incidence of childhood ADHD. In this paper, we mentioned the environmental risk factors that were most commonly associated with ADHD etiology.

2. Pre- and perinatal complications

Complications related to gestation, labor, and the neonatal period are the most common environmental risk factors that were associated with ADHD pathophysiology. Problems that occur before, during, or after birth were supposed to play a role in the development of ADHD. It has been supposed that the risk factors that affect brain development negatively in critical periods would have long-term effects on cognitive functions and behaviors [5]. ADHD has been associated with maternal smoking and alcohol consumption, emotional stress and medical diseases during pregnancy, and gestational complications as well as complications during labor, low birth weight, prematurity or postmaturity, early childhood physical trauma that could affect brain development negatively, and psychosocial challenges [6-9]. The complications that were associated with ADHD include gestational maternal health problems, toxemia or eclampsia, maternal age, intrauterine infections, fetal postmaturity or prematurity, difficult traumatic labor, fetal stress, low birth weight, prenatal bleeding, and all postnatal complications that can negatively affect brain development [9, 10]. Şenol et al. (2001) analyzed prenatal and perinatal histories of 121 patients with ADHD, 50 patients with oppositional

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defiant disorder (ODD), and 99 patients with conduct disorder (CD) and reported hypoxia in 5.6%, preterm labor in 9.3%, post-term labor in 4.4%, and unplanned pregnancy in 22.6% of the cases [11]. Prenatal, natal, and postnatal characteristics of the patients and the season of birth were investigated in an unpublished thesis study performed by us, and labor problems (difficult traumatic labor, maternal psychosocial stress and smoking, hypoxia, postnatal jaundice, gestational hypertension) and Cesarean section rate in ADHD group were found significantly higher than the control group [12]. Those findings are in accordance with the previous studies that reported low birth weight, and gestational and neonatal complications were risk factors for ADHD [13, 14].

Pre- and perinatal risk factors may cause hypoxic injury and neuronal developmental defects at the early developmental periods of the brain. Basal ganglions that have usually been linked to with ADHD are one of the most metabolically active structures of the brain, and they are sensitive to hypoxic injury [10]. Any perinatal injury to the frontal lobe has been reported to probably affect cognitive functions such as attention, motivation, and planning, and cause ADHD symptoms [15].

Although some studies reported a strong correlation between low birth weight and ADHD [16, 17], some other studies did not rule out potential familial confounding and gene-environment interactions [18-20], and suggested that children with low birth weight were more often inattentive, had social problems, and low self-esteem. Another study found that children who were born preterm were at risk for reduced cognitive test scores at school age [21]. A previous large twin study reported that birth weight accounted for less than one percent of the variance in ADHD symptoms, and it was not a major risk factor for ADHD [22]. Some previous studies reported that low birth weight affected inattention more than hyperactivity [17, 21]. However, a recent comprehensive twin study reported that a lower birth weight was significantly correlated with increased severity of all ADHD symptoms including inattention, hyperactivity-impulsivity, and total scores, and those findings supported the results of previous positive studies. This large recent study is important for demonstrating the correlation of low birth weight with ADHD, which remained after being controlled for gestational age, and shared environmental and genetic confounds [16]. In a longitudinal follow-up study it was found that low birth weight increased the development of ADHD 2.11-fold compared with the general population [23]. In accordance with these data, it could be concluded that low-birth weight is an important risk factor for the development of ADHD.

In a recent study that investigated the relation between maternal age at childbirth and risk for ADHD in the offspring, it was reported that women giving birth at younger ages (teenage mothers) were more likely to have children with ADHD. The relation of early maternal age with ADHD was explained by genetic confounding, which means genetic factors transmitted from mothers to children contributed to both mother's age of childbirth and ADHD in the offspring [24].

More gestational psychosocial stress was reported in mothers of the children with ADHD [8, 25]. Mother's depression, stress, or nervousness during pregnancy are associated with a broad spectrum of negative outcomes including emotional problems, ADHD symptoms, and defects in the cognitive development of the child. Prenatal anxiety and depression were supposed to

contribute 10–15% of the burden attributed to emotional and behavioral negative outcomes. The biological mechanisms underlying the relation of prenatal stress and negative outcomes in the child have been recently started to be enlightened. Exposure to prenatal stress was supposed to cause changes in the behavior of the child by increasing the levels of corticotropin releasing hormone, and by disturbing functions of hypothalamic pituitary adrenal (HPA) axis. Disturbed HPA functions were closely associated with neurobiological development and the risk for psychiatric disorders [25, 26]. Although increased exposure to high levels of cortisol in fetus was shown in animal models, some authors commented that HPA axis operated differently in humans, and responded to stress less as the gestational age increased [27]. On the other hand, some others reported that stress increased fetal transfer of maternal cortisol through placenta, decreased the levels of placental enzyme (11β-HSD2) that converted cortisol to inactive cortisone, and the cognitive development of the fetus was affected negatively as the cortisol levels in the amniotic fluid increased [27]. The sympathetic nervous system that is activated during stress was reported to decrease blood flow to the fetus by increasing the resistance of uterine artery, and a decreased blood flow could affect the brain development of the fetus [28]. Those findings may explain the relation of exposure to prenatal stress with the development of ADHD.

3. Prenatal maternal smoking

Prenatal maternal smoking was reported to be a risk factor for hyperactivity in the offspring. It was reported that 25% of the mothers who gave birth smoked in the United States, and only a small proportion of them quit smoking after they had learned that they were pregnant [29]. The rate of smoking during pregnancy was reported between 3% and 37% in Turkey [30-33]. Millberger et al. (1996) reported that 22% of children with ADHD had a history of prenatal cigarette smoke exposure whereas 8% of children without ADHD had the same exposure history. Smoking disturbs normal placental functions by decreasing uterine blood flow [34]. Decreased oxygen supply and nourishment of fetus results in hypoxia-ischemia and malnutrition [35]. As a result, intrauterine growth retardation occurs [36]. A number of studies reported that prenatal exposure to cigarette smoke affected pre- and postnatal growth negatively, damaged neuronal pathways, caused abnormalities in cellular proliferation and differentiation, inhibited development of cholinergic and catecholaminergic systems, and hence increased the risk for cognitive developmental defects and behavior problems in children and adolescents [37, 38]. Prenatal exposure to nicotine stimulates fetal pre-synaptic high affinity $\alpha_4\beta_2$ neuronal nicotinic receptor complex, and alterations appear in neurite growth and branching through DRD4 receptors as a result of increased release of dopamine (DA) from the dopaminergic neurons. Those developmental changes in neuronal maturation result in permanent alterations in neuronal organization and functions [39]. Milberger et al. (1998) found that maternal smoking increased the risk of ADHD by 2.7-fold [36]. A subsequent study by Hjern et al. (2010) reported that maternal smoking during pregnancy increased ADHD prevalence by 2.86-fold [40]. Interestingly, Han et al. (2014) showed that a non-smoking mother's exposure to environmental tobacco smoke, which reflected paternal smoking during

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pregnancy, was also associated with increased risk of ADHD [41]. Kotimaa et al. (2003) reported a dose-response relationship between maternal smoking during pregnancy and hyperactivity [42].

Dopaminergic and noradrenergic systems were found to be hypoactive and unresponsive to exogenous stimulation after prenatal nicotine exposure [43]. Prenatal nicotine exposure was also shown to decrease nicotine-triggered norepinephrine release [44]. It has been supposed that this disturbance in the development of catecholaminergic system may be related to increased ADHD prevalence [10].

The interactions of environmental factors with genetic factors are important for the clinical presentation and developmental course of ADHD. DRD4 7 repeat allele is the most commonly associated allele with ADHD, and it is known that it increases the sensitivity of the child to environmental factors [45]. Neuman et al. (2007) reported that prenatal cigarette smoke exposure caused more severe ADHD symptoms in subjects carrying DRD4 7 repeat allele [46]. Subsequently, a similar study performed by Altink et al. (2008) did not find any significant gene-environment interaction [47]. When the relation of DAT1 gene with ADHD was considered, Neuman et al. (2007) reported that the odds ratio for ADHD was 2.9 among twins with DAT1 440 allele and prenatal cigarette smoking exposure. The odds ratio for ADHD was 3.0 among twins with DRD4 7 repeat allele who were exposed to prenatal cigarette smoke [46]. In a subsequent study conducted by Becker et al. (2008), it was shown that neither DAT1 nor prenatal cigarette smoke exposure was related to ADHD symptoms; however, males exposed to prenatal cigarette smoke and homozygous for DAT1 gene 10 repeat allele had higher hyperactivity-impulsivity [48]. On the other hand, further maternal risk factors (young age, low level of education, poor prenatal care, maternal behavioral problems) besides maternal smoking were supposed to be influential for the relation between nicotine and ADHD in addition to a direct cause-and-effect relationship [49].

In summary, it is now known that prenatal nicotine exposure is an important environmental risk factor for the development of ADHD. The next step will be to determine which epigenetic mechanisms are responsible.

4. Prenatal alcohol exposure

Maternal alcohol consumption is one of the risk factors for the development of ADHD. Prenatal alcohol exposure is neurotoxic and gives rise to brain abnormalities [50, 51]. Prenatal alcohol exposure increases the risks for hyperactivity, destructive-offense oriented or impulsive behavior, and psychiatric disorders in children. Disturbed cognitive abilities include overall intellectual performance, learning and memory, language, attention, reaction time, visual-spatial abilities, executive functions, fine and gross motor skills, and adaptive and social behaviors [52]. Streissguth et al. (1990) reported that moderate levels of prenatal alcohol exposure might have long-lasting effects on IQ, and led to learning problems in school aged children [53].

Various studies showed that prenatal alcohol exposure increased the risk for ADHD [41, 54]. Some other studies did not report any association between prenatal alcohol exposure and Continuous Performance Taskperformance in school aged children [55]. Similarly, Rodriguez et al. (2009) did not report any significant association between ADHD and prenatal alcohol exposure [56]. In another study, maternal alcohol consumption was suggested to be associated with a higher rate of conduct problems, but not with ADHD [57]. In a recent review article, it was suggested that heavy prenatal alcohol exposure was associated with symptom characteristics of ADHD including externalizing problems, inattention, impulsivity, as well as the diagnosis of ADHD. However, the association of low to moderate levels of prenatal alcohol exposure with ADHD was less conclusive [58]. The data so far indicate that there is no strong evidence showing that prenatal alcohol exposure plays as much of a role in the development of ADHD as prenatal nicotine exposure. Therefore, longitudinal follow-up studies with large samples are needed to understand the exact effect of prenatal alcohol exposure on ADHD development.

5. Prenatal substance exposure

Various studies showed that gestational exposure to cocaine was associated with behavioral problems and attention disorders in preschool and school aged children [59]. Exposure to cocaine may cause behavioral alterations by changing the monoaminergic system [58]. Disruption of the monoaminergic system's development in the prenatal period may result in changes in various cognitive and behavioral processes such as emotional regulation, arousal, and attention [60]. Cocaine exposure in the first trimester was reported to be significantly associated with increased behavioral problems in 3-year-old children [61]. Another study evaluated 6-year-old, cocaine and non-cocaine exposed children's mental health outcomes, and showed that cocaine exposed children were more likely to self-report ADHD and oppositional defiant disorder symptoms [62]. A large maternal lifestyle study performed by Bada et al. (2011) reported that prenatal cocaine exposure as declared by teacher and parents predicted (or was associated with) externalizing behavior problems in preadolescent children [63].

In a series of studies, Richardson et al. showed that prenatal cocaine exposure was associated with neurobehavioral and neurophysiological alterations at birth [64], temperament at 1 year [65], and temperament, memory, and behavior at 3 years of age [61]. Same authors reported that children exposed to cocaine during pregnancy had more behavior problems at 7 years of age when compared to the children of women who stopped using cocaine at pregnancy's early stages or who never used cocaine prenatally. Therefore, it was emphasized that third trimester use reflecting use throughout pregnancy was associated with significantly more externalizing behavior problems and inattention [66]. On the other hand, follow up analysis performed when the children were 10 years old did not show any significant effect of prenatal cocaine exposure on externalizing problems [67]. As it was commented, the latter result indicated that the results of prenatal cocaine use might differ in relation with methodological factors such as the type of assessment and observer [67], as well as developmental stage [58].

The data on the long-term effects of heroin use are more scarce [58]. Wilson et al. (1979) reported parent-reported uncontrollable tempers and impulsiveness in 3- to 6-year-old children exposed to prenatal heroine, and indicated that those children were more hyperkinetic [68]. Another study reported that children with prenatal methadone exposure were considered to have parent-reported hyperactivity and externalizing behavior problems [69].

Slinning (2004) reported that foster placed children prenatally exposed to poly-substances had significantly elevated levels of impulsivity and attention problems at preschool ages [70]. The presence of environmental changes in studied children such as adoption or accommodation in foster care homes, and comparing those children with healthy controls living together with their biological parents appear as limitations of the studies investigating the effects of prenatal substance exposure on behavior and the attention of children. On the other hand, living with foster-parents may imply the presence of an adequate care, and it may be considered as a protective factor against postnatal risk factors. Contrary to this hypothesis, Ornoy et al. (2010) reported that adoption did not relieve the effects of prenatal exposure to drugs [71]. Another study showed that children born to heroin-dependent parents and raised at home had lower cognitive abilities and higher attention problems at preschool and school ages. However, children who were born to heroin-dependent mothers, adopted, and being raised in an ideal environment had high frequencies of attention and behavioral problems, but normal intellectual functions. Finally, it was found that all school aged children born to heroin-dependent parents including the ones raised at home and adopted had a high rate of ADHD, but an ideal environment after birth had a positive effect on intellectual abilities [72]. Although this result was interpreted as ADHD symptoms might be directly associated with heroin exposure and originated from fetal brain injury related to heroin [71, 72], the high incidences of hyperactivity and inattention in children born to heroin-dependent fathers [72] suggest that different environmental factors contribute to this association.

When it is considered that caretaker characteristics, home environment, and community factors are also risk factors for later behavior problems [63], it is clear that prenatal substance abuse may be a predisposing factor for those risk factors as well as other environmental risk factors such as presence of other maternal psychopathologies, malnutrition during pregnancy, exposure to other abused substances, and unfavorable postnatal living conditions.

6. Toxins and food additives

Various toxins and food additives were investigated in the etiology of ADHD. Exposure to toxins such as lead, mercury, and manganese, or food additives such as dyes and preservatives, as well as sugars was reported to result in the development of ADHD [73-75]. Braun et al. (2006) reported that higher blood lead concentrations in children had a significant correlation with ADHD, and children with a blood lead level >2.0 μg/dL had 4.1-fold increased risk for ADHD [76]. It was emphasized that blood lead levels under 10 μg/dL which is the level set by Centers for Disease Control and Prevention was associated with an increased risk of ADHD in children [76, 77]. Exposure to lead and polychlorinated biphenyls (PCBs) was shown to

cause cognitive deficits similar to those seen in children with ADHD, and disturbed attention and executive functions [78]. Studies on children and animal models indicated that lead disrupted both response inhibition and attention processes [79-81], however PCBs tended to disturb response inhibition to a greater degree than attention [78, 82-84]. In a recent study, Neugebauer et al. (2015) investigated the effects of prenatal polychlorinated dibenzo-p-dioxins and furan (PCDD/F), PBC, and lead exposure on attention performance in school-aged children [85]. They found that pre- and perinatal PCDD/F and PBC exposure might affect attention performance in healthy children at low environmental levels while PCDD/F or PBC exposure were negatively associated with ADHD-related behavior, and prenatal lead exposure had an effect on attention deficits [85]. However, cumulative findings on the association between lead exposure and attention deficits are less consistent.

The data on relation of environmental mercury exposure and ADHD are not consistent [86-88]. A recent meta-analysis by Yoshimasu et al. (2014) suggested that environmental perinatal mercury exposure (exposure sources were air pollution, maternal fish consumption during pregnancy estimated by maternal hair samples, or childhood environmental exposure measured by blood sample) was significantly associated with an increased risk of ADHD. On the other hand, the mercury exposure of embryos or young infants related to thimerosal containing vaccines were not associated with an increased risk for ADHD [89]. Studies that investigated the association between postnatal pyrethroid pesticide exposure and ADHD revealed diverse findings. Rodríguez (2012) reported a correlation between urine levels of pyrethroid pesticide's metabolite 3-phenoxy-benzoic acid (3-PBA) and ADHD in girls [90] whereas Quirós- Alcalá et al. (2014) showed that postnatal pyrethroid exposure was not associated with the parental report of ADHD in children [91].

In fact, exposure to those toxins and food additives cannot be determined in many of the children with ADHD, and many children who are exposed to those substances do not develop ADHD. Therefore, scientific evidence related to those substances need to be further clarified [10].

7. Season of birth

It was suggested that season of birth was one of the environmental risk factors. It was reported that season of birth paved the way for seasonal viral infections, and it might play an important role in the etiology and pathophysiology of ADHD [92]. Chotai et al. (2003) reported that season of birth variations were different for schizophrenia and affective disorders in tryptophan hydroxylase, serotonin transporter, and DRD4 gene polymorphisms. Therefore, it was reported that season of birth could be a confounding variable when investigating the role of the candidate genes in susceptibility to psychiatric disorders [93]. Being born in spring or summer was associated with an increased risk for neurodevelopmental disorders [94]. This period was associated with the presence of a short sunlight time for a long period and decreased sex hormones as well as increased pineal gland activity and melatonin release. Melatonin is synthesized from serotonin by N-acetyltransferase enzyme. Melatonin synthesis

peaks at night, and it is at minimum during the day. It has been supposed that melatonin inhibits DA synthesis in many regions of the brain including striatum, and DA inhibits melatonin production via DRD4. It was reported that melatonin-DA interaction during pregnancy might result in decreased postsynaptic DRD4 receptor sensitivity [95]. Mick et al. (1996) reported significant relations of winter births and ADHD children with learning disabilities, and no psychiatric comorbidity [92]. Some studies investigated the relation between DRD4 gene and season of birth. Seeger et al. (2004) performed a study on patients with ADHD and comorbid DB, and claimed that seven-repeat allele could be associated with a relative risk only in the ones who were born in summer [96]. On the contrary, another study by Brookes et al. (2008) found a significant relation between winter births and seven-repeat allele in a large sample group [97].

In conclusion, in light of these data, it is not clear that any of the birth seasons are related to an increased risk for ADHD development. The main reason for the inconsistent results in this area might be that the birth season has an indirect effect on ADHD by affecting the exposure to other environmental risk factors such as seasonal viral infections or hormonal changes. When the role of gene-environment interactions and various epigenetic mechanisms on ADHD etiology are taken into account, it is obvious that there is a need to consider all these interactions and the effects of secondary environmental factors on the results.

8. Iron deficiency

The relation between iron deficiency and ADHD symptoms was investigated in some studies [98]. A direct correlation was proposed between iron and dopamine dysfunction, which was suggested to be the case in ADHD. Iron is a cofactor of tyrosine hydroxylase enzyme that plays a role in the rate limiting step of dopamine synthesis [99], and animal studies showed that iron deficiency could affect dopamine receptor density in brain [100]. Konofal et al. (2004) reported low ferritin levels in 84% of the children diagnosed with ADHD, and found a negative correlation between ferritin levels and ADHD symptom severity [101]. Another study found a correlation between low ferritin levels and hyperactivity scores in children with ADHD, however no relation was found with cognitive functions [102]. Karakurt et al. (2011) reported a significant negative correlation between behavior problems and ferritin levels in children with ADHD [98].

Although the results of studies are conflicting, iron supplementation was reported to decrease ADHD symptoms [103]. A large study that investigated the effects of iron deficiency and ferritin levels on treatment of ADHD with stimulants reported that neither iron deficiency nor ferritin levels had significant correlations with short-term response to stimulant therapy, and the authors claimed that the relation between iron metabolism and ADHD was more complex contrary to the popular belief [104].

The results of the researches investigating the relationship of iron deficiency with ADHD etiology show promise and form the basis of further studies to investigate the levels of iron in brain tissue by various neuroimaging methods or classified patients according to the factors

that may affect the iron parameters in different ways. However, in this instance, before drawing any conclusions in this area, there is a need for further research.

9. Psychosocial stress factors

Psychosocial challenges such as maltreatment, emotional trauma, and sexual abuse were correlated with ADHD development [105, 106]. Familial factors associated with childhood mental disorders including severe marital discord, low social status, a large family, paternal criminality, maternal mental disorders, lack of family consolidation, and living in nursing homes were described as adversity factors [7]. In a recent retrospective study that aimed to determine the parameters predictive of later diagnosis of ADHD in infants and toddlers, one of the identified factors was psychosocial risk factors, including stress, marital conflicts, separation and divorce, and maternal depression [107]. In a systematic review that investigated environmental risk factors for disruptive behavior disorders (ADHD, ODD, CD), psychosocial risk factors such as parental stress, maternal depression, early deprivation, separation, and adoption were reported to be associated with disruptive behavior disorders [108]. In a prospective cohort study conducted with the general population and consisting of 2,057 children followed up from 5 months to 8 years, as well as other various environmental risk factors, three important psychosocial risk factors were found to be associated with ADHD development: non-intact family, paternal history of antisocial behavior, and maternal depression [23]. Comparison of the families with children with ADHD and the families without children with ADHD revealed more interpersonal conflicts, increased maternal stress and marital discord, separation and divorce, less family dialogues and positive family experiences in ADHD families [109]. In a study investigating how early-life deprivation might cause ADHD, it was reported that early-life deprivation disrupted cortical development and caused reduced cortical thickness and atypical functioning in regions associated with regulation of attention. The increased rates of ADHD among children raised in institutional settings were reported to be possibly associated with this mechanism [110].

Although some authors did not believe in a causative role of parental discipline on the development of ADHD [111], some others believe that discipline problems played an important role in the development of ADHD symptoms, and observing behavior problems and oppositional defiant disorder in children with ADHD [112]. Gathering negative factors rather than the presence of any of those factors was reported to affect development in a negative way. Psychosocial factors were reported to have effects on preparation and fast manifestation in the development of ADHD [113].

10. Conclusion

The most important challenges in studies investigating the environmental factors in ADHD etiology include subjectivity of retrospective assessment, common intermingling of the risk

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factors, possibility of observer bias, and methodological differences among studies. However, the results of most current studies grew stronger owing to prospective and longitudinal study design, obtaining information from multiple sources such as parents and teachers, use of standardized scales, planning of the study by considering secondary and even tertiary risk factors in addition to the primary risk factor, and analyzing multiple factors in statistical analysis. In this regard, the cumulative evaluation of all studies performed to date indicates the significance of environmental risk factors in the development of ADHD. However, while some of these environmental risk factors are well established, others still require more investigation. Although the association of pre- and perinatal complications that cause hypoxic injury, low birth weight, prenatal nicotine exposure, various perinatal psychosocial risk factors such as maternal depression and parental stress with etiology of ADHD are more clear, the study results associated with prenatal alcohol exposure, toxins, and food additives or iron deficiency are contradictory.

In summary, different from the other etiologic factors, relatively controllable and preventable characteristics of environmental risk factors put forward their importance once again. Determination of the environmental risk factors that play a role in the etiology of ADHD and other neurodevelopmental disorders is important for possible prevention of those diseases, as well as for the execution of comprehensive interventions starting from early developmental stages, and for taking necessary precautions.

Author details

Esra Guney[1], Fatih Hilmi Cetin[2] and Elvan Iseri[1]

1 Department of Child and Adolescent Psychiatry, Gazi University Medical Faculty, Ankara, Turkey

2 Department of Child and Adolescent Psychiatry, Kayseri Training and Research Hospital-Emel Mehmet Tarman Children's Clinic, Ankara, Turkey

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