

Environmental risk factors for attention-deficit hyperactivity disorder

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is the most common cognitive and behavioural disorder diagnosed among school children. It is characterized by deficient attention and problem solving, along with hyperactivity and difficulty withholding incorrect responses. This highly prevalent disorder is estimated to affect 5–10% of children and in many cases, persists into adulthood, leading to 4% prevalence among adults. Converging evidence from epidemiologic, neuropsychology, neuroimaging, genetic and treatment studies shows that ADHD is a valid medical disorder.

The majority of studies performed to assess genetic risk factors in ADHD have supported a strong familial nature of this disorder. Family studies have identified a 2- to 8-fold increase in the risk for ADHD in parents and siblings of children with ADHD. Various twin and adoption studies have also highlighted the highly genetic nature of ADHD. In fact the mean heritability of ADHD was shown to be 0.77, which is comparable to other neuropsychiatric disorders such as schizophrenia or bipolar disorder.

However, several biological and environmental factors have also been proposed as risk factors for ADHD, including food additives/diet, lead contamination, cigarette and alcohol exposure, maternal smoking during pregnancy, and low birth weight. Many recent studies have specifically examined the relationships between ADHD and these extraneous factors. This review describes some of these possible risk factors.

Conclusion: Although a substantial fraction of the aetiology of ADHD is due to genes, the studies reviewed in this article show that many environmental risk factors and potential gene–environment interactions also increase the risk for the disorder.

BIOLOGICAL ADVERSITY

Diet

The idea that certain foods might cause attention-deficit hyperactivity disorder (ADHD) has received much attention in the popular press. Several researchers claimed to have cured ADHD by eliminating food additives from the diet. The Feingold diet for ADHD was popularized by the media and accepted by many parents of ill children as a testament to this claim. Systematic reviews, however, showed that the diet was not effective and concluded that food additives do not cause ADHD (1).

Exposure to toxins

In contrast to the mostly negative studies of dietary factors, some toxins have been implicated in the aetiology of ADHD. Several groups have shown that lead contamination leads to distractibility, hyperactivity, restlessness and lower intellectual functioning that are very similar to the disease profile in ADHD (2). However, most ADHD children do not show lead contamination and many children with high lead exposure do not develop ADHD. Mercury and manganese are considered to be the other developmental toxicants related to the development of ADHD symptomatology. Mercury (Hg) is a potent neurodevelopmental

toxicant commonly encountered as dietary methylmercury. Small prenatal exposures resulting from maternal consumption of contaminated fish in New Zealand (mean maternal hair level Hg 8.3 ppm) and the Faroe Islands (mean maternal hair level Hg 4.3 ppm) adversely affected IQ, language development, visual-spatial skills, gross motor skills, memory and attention in offspring (3). The developmental neurotoxicity of manganese has emerged as a significant public health concern in recent times. In small epidemiologic studies of children, manganese hair levels are associated with ADHD (4). Moreover, developmental exposure to manganese in laboratory animals is associated with hyperactivity.

Another developmental toxin that has been widely studied is the class of compounds known as the polychlorinated biphenyls (PCBs). PCBs are a family of 209 manufactured compounds (congeners) that were once produced on a large scale in the United States for use as heat-resistant electrical insulators, brake liners, paints, sealing compounds, etc. They are highly stable, bioaccumulate, and because of their stability have entered the food chain. When ingested, PCBs are readily absorbed, and because they are lipophilic and resistant to metabolism, they can persist in fat tissue and human breast milk (5). The pathologic physiology of congenital PCB poisoning is characterized by intrauterine growth retardation, brown staining of the skin and mucous membranes, natal teeth, widely open fontanelles and sagittal sutures and apparent overgrowth of the gingiva (6). The neurodevelopmental effects of PCBs have also been extensively studied. There have been cohort studies, such as the Dutch cohort, the Oswego cohort, the Michigan cohort, the German cohort and the Yu-Cheng cohort, which were conducted in infants from birth till 7 years of age. Studies have also been done in adolescents and adults. All these studies have, to varying degrees, related prenatal PCB exposure to poorer concentration or focused attention, less accurate performance and slower mean reaction time (7).

A number of studies have been done to test for the effects of PCB exposure on rodents at different stages, perinatally and adult. Holene et al. (8) showed that rats postnatally exposed to PCB congeners 153 and 126 showed higher frequency of lever presses that denoted hyperactivity. Chronically or acutely applied PCB 153 is also known to significantly reduce LTP in the CA1 region of the hippocampus at age 30–60 days (corresponding to early adolescence and early adulthood, respectively). In CA3, PCB 153 reduced LTP in 30-day animals but potentiated it in 60-day animals. The cellular and molecular basis of PCB-induced neurotoxicity is still unclear. Basha et al. (9) have shown that PCB mediates its effects through changes in Ca^{2+} homeostasis and an increase in the binding of transcription factors, such as AP-1, Sp1 and NF- κ B, to DNA in the hippocampus and cerebellum. AP-1 DNA binding is inversely related to the degree of maturation of a brain area. The effects of PCBs have also been related to apoptosis. Ortho-substituted PCBs and hyperactivity may be related by PCBs' ability to directly alter dopamine levels. One group of studies found reduced levels of cellular dopamine in PCB-exposed PC 12 cells (10). In vivo studies with mice (11), rats and monkeys (12) also

show reduced levels of dopamine in the brains of exposed animals. The loss of dopamine would mimic the pathophysiological state of ADHD.

Pregnancy and delivery complications

The literature examining the association of ADHD with pregnancy and delivery tends to support the idea that these adverse events can predispose children to ADHD (13). Specific complications implicated in ADHD include toxemia or eclampsia, poor maternal health, maternal age, foetal postmaturity, duration of labour, foetal distress, low birth weight and antepartum haemorrhage. Notably, the basal ganglia, which are commonly implicated in ADHD, are also among the most metabolically active structures in the brain, and are particularly sensitive to hypoxic insults.

Foetal exposure to alcohol

The most common and most serious consequence of maternal drinking during pregnancy is foetal alcohol syndrome (FAS), characterized mainly by mental retardation, abnormal facial features and a small head size. Although ADHD and FAS are two very separate disorders, the ADHD-like behavioural component of FAS suggests that alcohol might have a causal role to play in ADHD.

Prenatal alcohol exposure is known to induce brain structural anomalies, especially in the cerebellum (14). Microcephaly and Purkinje cell loss results from a single-day exposure to alcohol during the brain growth spurt period (human third trimester development; 15).

Prenatal alcohol exposure gives rise to many behavioural and cognitive problems. Children exposed to prenatal alcohol are rated to be hyperactive, disruptive, delinquent or impulsive and are at an increased risk for a range of psychiatric disorders and psychosocial deficits. Cognitive abilities that are impaired include overall intellectual performance, learning and memory, language, attention, reaction time and visuospatial abilities, executive functioning, fine and gross motor skills, and adaptive and social skills (16).

Foetal alcohol exposure studies done in children of different age groups show different effects. In school children of 7½ years, Streissguth et al. showed that an average of two drinks per day could lead to a 7-point decrement in IQ (17). At 14 years of age, subjects with exposure to alcohol in utero showed problems with attention, speed of information processing and learning problems, especially arithmetic (18). Baer et al. (19) reported that prenatal alcohol exposure is significantly associated with alcohol problems at 21 years of age. Based on a female twin study, Knopik et al. (20) concluded that parental alcoholism presented increased risk of offspring ADHD. Significant associations were found between maternal alcohol abuse and child ADHD (OR 2.04; 95% CI 1.24–3.39), maternal alcohol dependence and child ADHD [OR 3.19; 95% CI 1.67–6.10].

Some studies have not shown an association between prenatal alcohol exposure and ADHD-like neurobehavioural deficits in exposed offspring. In one such study Boyd et al. failed to show any adverse effect of foetal alcohol exposure on sustained attention performance in school children (21).

The mechanisms of the adverse effect of alcohol on early brain have been widely studied. Ikonomidou et al. (22) showed that rates of apoptotic neurodegeneration in the forebrain were greater in ethanol-treated rats than in rats treated with saline. Connor et al. (23) performed a functional magnetic resonance imaging (fMRI) study that suggested that a working memory task was more difficult for prenatally alcohol-exposed adults, requiring greater involvement of the dorsolateral prefrontal cortex.

Foetal exposure to maternal smoking

In the United States, tobacco use occurs in about 25% of all pregnancies (24). Several reports have established that maternal tobacco smoking during pregnancy adversely affects pre- and postnatal growth and increases the risk of foetal mortality, cognitive development and behaviour of children and adolescents (25).

Prenatal and postnatal effects of maternal smoking have been extensively studied. Gusella et al. (26) reported a decrease in motor scores and in verbal comprehension of prenatally nicotine-exposed 13-month-old offspring. Milberger et al. (27) found a 2.7-fold increased risk for ADHD associated with maternal smoking in 140 cases and 120 controls. Another study reported a 2-fold increased risk for ADHD associated with prenatal exposure to tobacco use (28). Kotimaa et al. (29) reported strong evidence for a dose-response relationship between maternal smoking during pregnancy and hyperactivity (OR 1.30; 1.08–1.58). Twin studies (30) found a strong contribution of genetic factors with regard to ADHD symptoms, on top of which maternal smoking during pregnancy explained additional variance.

Negative findings have also been reported. Eskenazi et al. (31) could not establish a dose-response relationship between in utero nicotine exposure and cognitive performance or activity level in children aged 5 years. Hill et al. (32) also did not show any association between maternal smoking and the risk for child and adolescent psychiatric disorders.

Animal studies have consistently shown lower birth weight in offspring exposed to nicotine prenatally when compared with nonexposed offspring (31). Low birth weight is a known risk factor for ADHD (33). Studies in animals have reported cognitive impairment associated with prenatal exposure to nicotine (34).

Cigarette smoke interferes with normal placental function, reducing uterine blood flow. The foetus is deprived of nutrients and oxygen, resulting in episodic foetal hypoxia-ischaemia and malnutrition (35), which may result in intrauterine growth retardation often seen in infants born to smoking mothers (16). Carbon monoxide and ingredients in tobacco tar can directly affect the foetal brain (24).

Nicotine directly stimulates nicotinic acetylcholine receptors (the most abundant being the $\alpha 4\beta 2$ and $\alpha 7$ subtypes in the brain). Direct actions of nicotine on the foetal brain were reported to induce abnormalities in cell proliferation and cell differentiation in mice and rats (36). Abnormalities in cell proliferation and differentiation have been shown to lead to regionally specific abnormalities in cell number and macromolecular content (37). Nicotine exerts its effects on

various neurotransmitter systems. In fact, the dopaminergic and noradrenergic systems have been found to be hypoactive and hypo-responsive to exogenous stimulation after prenatal exposure to nicotine at PND 30 (38). Prenatal nicotine treatment was also shown to produce a significant reduction in nicotine-induced release of norepinephrine (39). These disruptions in the development of catecholaminergic systems may explain the increased incidence of ADHD individuals prenatally exposed to nicotine because they are consistent with the hypothesis that hypodopaminergic synapses lead to ADHD and with the observation that drugs that increase either dopaminergic or noradrenergic transmission are therapeutic for ADHD.

PSYCHOSOCIAL ADVERSITY

Characterization of psychosocial risk factors for ADHD can help identify etiological risk factors associated with ADHD, and can also identify early predictors of persistence and morbidity of this disorder. The best example of the delineation of psychosocial factors for childhood mental disorders comes from Rutter's now classic studies of the Isle of Wight and the inner borough of London (40). These studies examined the prevalence of mental disorders in children living in two very different geographical areas and revealed six risk factors within the family environment that correlated significantly with childhood mental disturbances: (a) severe marital discord (b) low social class (c) large family size (d) paternal criminality (e) maternal mental disorder and (f) foster placement. This work found that it was the aggregate of adversity factors, rather than the presence of any single one, that impaired development.

Maltreatment and emotional trauma are also significantly correlated with childhood mental disturbances. In a study conducted by Famularo et al. (41) children who had suffered maltreatment exhibited significantly greater incidences of ADHD, oppositional disorder and post-traumatic stress disorder (PTSD) diagnoses than the controls. Mcleer et al. (42) found the most frequent diagnosis of sexually abused children to be ADHD (46%). Some of the symptoms exhibited by maltreated and traumatized children are problems concentrating, hypervigilance to perceived fear stimuli, avoiding stimuli associated with trauma and sleep disturbance (43). Other symptoms include excessive worry, denial, rage and social withdrawing. Some of these symptom manifestations can be grouped under the ADHD categories of inattention, hyperactivity and externalizing behaviours (44), and show considerable overlap with PTSD (45). In a recent study, Hartl et al. (46) reported significantly greater symptoms of inattention and hyperactivity among compulsive hoarders. Possessions appeared to be associated with safety, suggesting that hoarding participants might have experienced more traumas in their lives and use possessions as a source of comfort.

Other cross-sectional and longitudinal studies have identified variables, such as marital distress, family dysfunction, low social class, chronic conflict, decreased family cohesion and exposure to maternal psychopathology as risk factors for psychopathology and dysfunction in children (47).

DOES WATCHING TELEVISION CAUSE ADHD?

Cross-sectional studies have suggested that television viewing is associated with psychopathology in children. For example, a cross-sectional survey of students in grades 2 and 3 reported that higher levels of television viewing were associated with poor social and school achievement, and with greater psychopathology in several areas as measured by the Child Behavior Checklist: thought problems, attention problems, delinquent behaviour and aggressive behaviour (48). But such studies are very difficult to interpret because they can establish association but not causality.

To remedy this problem, Christakis et al. (49) used a longitudinal study to assess the effects of early television exposure (at ages 1 and 3) on attention problems at age 7 in 1345 children. Ten percent of children had attention problems at age 7 and the number of hours of television viewed each day at both ages 1 and 3 was associated with age 7 attention problems. The odds ratios were 1.09 for both age predictions. An increase of 1 SD in how many hours of television children watched at age 1 predicted a 28% increase in probability of having attention problems at age 7.

Although intriguing, these results were difficult to interpret for several reasons. The authors did not include a standard measure of ADHD, and some of the items constituting their attention problems measure were not ADHD symptoms (e.g. 'easily confused' and trouble with obsessions). Christakis et al. defined attention problems as being 1.2 SDs above the mean, which implicitly assumes that the population prevalence is about 20%, which we know is not true (50).

Obel et al. attempted to replicate these findings in a birth cohort of all children born from 1990 at the Aarhus University Hospital, Denmark (51). They evaluated whether the amount of time spent watching television at 31/2 years of age predicted attention problems at ages 10–11. They found no significant association between hours of watching television and behavioural problems.

An 18-month longitudinal study compared 59 ADHD children with 106 non-ADHD children on laboratory measures of visual attention to television, cognitive engagement to televised stories, factual recall of televised stories, and causal recall of televised stories and parental reports of a child's weekly television viewing (52). Among the non-ADHD children, baseline television viewing predicted poor visual attention and low cognitive engagement 18 months later. These patterns were not observed among ADHD children. This work suggests that rather than causing ADHD, television viewing may lead to more subtle cognitive defects, the clinical significance of which needs to be established.

Another study that attempted to replicate the findings of Christakis et al. examined two samples of 2500 children, which were randomly selected from a longitudinal study (53). Although the study did not include a standard measure of ADHD, it did have a measure that reflected ADHD symptoms. The authors tested the hypothesis that television viewing in the kindergarten years would predict ADHD symptoms during the first grade. In both samples, the authors found a small, nonsignificant association between tele-

vision viewing and ADHD symptoms. They also reported that parental limits on television watching did not predict subsequent levels of ADHD symptoms.

GENE-ENVIRONMENT INTERACTION IN ADHD

The heritability of ADHD is estimated to be about 77%. A number of susceptibility gene variant findings for ADHD (dopamine D4 and D5 receptors, COMT, dopamine transporter, and SNAP-25) have been independently validated and meta-analyses have yielded significant evidence of association (54). The course of this disorder, however, cannot be solely explained by genes. A number of environmental factors, some of which have been listed above, appear to be significantly associated with ADHD. In fact, more often than not, the symptomatology of an individual is the result of interplay between an individual's genes and his or her environment.

Gene-environment interaction ($G \times E$) describes any phenotypic events that are due to interactions between the environment and genes. In $G \times E$, genes operate by influencing response to environmental factors. Till date, few molecular genetic studies have addressed the connection between $G \times E$ and ADHD. One gene-environment study was done on children who showed conduct disorder symptoms in ADHD and also carried the COMT gene risk variant. Results showed that these kids were more susceptible to the adverse effects of lower birth weight (55). Another group, studying the association between prenatal smoking exposure and ADHD subtypes, showed that the odd of diagnosis of DSM-IV-combined subtype was 2.9 times greater in twins who had inherited the DAT1 440 allele and who had prenatal exposure to smoke, than in unexposed twins without the risk allele (56). A study done by Kahn et al. suggested that child hyperactivity and impulsivity were associated with the 480-bp DAT1 risk allele only when a child also had exposure to maternal prenatal smoking (57). In another recent prospective study done on children with ADHD from southeast England and Taipei, Taiwan, a stronger association was found between a DAT1 haplotype and ADHD when the mother had consumed alcohol during pregnancy (58). In a study done by Jacobson et al., the results showed that the absence of maternal ADH1B*3 allele and prenatal exposure alcohol was associated with higher ratings of ADHD symptoms and other problem behaviours in children born to these mothers (59).

The above studies suggest that $G \times E$ interactions may be the reason for the phenotypic complexity of ADHD. This disorder might have its origins in genes but the course of the disorder is probably influenced by the way these genetic factors interact with and affect an individual's response to the environment.

SUMMARY AND CONCLUSIONS

Although a substantial fraction of the aetiology of ADHD is due to genes, the studies reviewed in this article show that many environmental risk factors and potential gene-environment interactions also increase the risk for the

Table 1 Risk factors associated with ADHD

Diet	0
PCB	++
Foetal exposure to alcohol	++
Maternal smoking	++
Pregnancy and delivery complications	+
Psychosocial adversity	+
TV viewing	0

0 = no positive evidence of association reported till date; + = nonsignificant evidence of association; ++ = significant evidence of association.

disorder. Although dietary factors have not been shown to increase the risk for ADHD, exposure to substances, such as lead, cigarette smoke, alcohol and PCBs has been shown to increase risk across several studies, and foetal exposure has been established as a critical period for increasing that risk. Pregnancy and delivery complications leading to hypoxia have also been implicated in many studies as has low birth weight. Psychosocial adversity in the home environment and low social class also appear to play a role in the aetiology of the disorder. In contrast, viewing television has not been shown to be a significant risk factor for ADHD (Table 1).

It is notable that many of the environmental risk factors for ADHD occur early in development, which is consistent with the idea that ADHD is a neurodevelopmental condition. Also notable is that, with the exception of rare cases (such as ADHD secondary to closed head injury), both the genetic and environmental risk factors for ADHD have small, incremental effects on the expression of the disorder. Future work needs to determine whether modifying environmental risk factors can lead to preventive interventions, and there is a big gap in our knowledge about the mechanisms whereby genes and environment combine to produce ADHD.

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