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Review Article

Systematic review of risk factors associated with attention deficit hyperactivity disorder

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Abstract

Introduction: Attention deficit hyperactivity disorder (ADHD) is complex in its etiology and its manifestations. This systematic review will critically analyze the latest research regarding risk factors associated with ADHD such as environmental, including preterm birth, smoking, and prenatal alcohol use. Furthermore reviewed, will be articles researching genetics, such as dopamine active transporter (DAT1), LPHN3, as well as genetic-environmental interaction for precursors of ADHD.

Discussion: Current theories of ADHD show evidence supporting multiple genetic and environmental factors that interact during early developmental stages in the fetus to create a neuro-biological susceptibility to ADHD. The DAT1 has been implicated in ADHD although the mechanism by which it exerts its effects remains unknown. Factors due to drinking, smoking or stress while pregnant can affect the nervous system, which later may be linked to ADHD symptoms because they may alter genes during development by causing a genetic variation.

Conclusion: Future research could benefit from using prospective, longitudinal studies, with large sample sizes. With contradictory results and many competing theories about precursors of ADHD, more research using advanced genetic technology will help researchers learn more about ADHD's complex risks, precursors, and symptoms.

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Introduction

Multiple environmental risk factors have been examined to determine, which factors have a significant relationship with developing attention deficit hyperactivity disorder (ADHD) such as prenatal smoking, alcoholism and preterm birth. There is significant evidence that genetics can also explain much of the variability in terms of susceptibility to ADHD.[1-3] Recent studies have also examined a membrane-spanning protein that mediates the reuptake of dopamine (DA) from the synapse DA active transporter (DAT1) and the neuronal pathways of frontostriatal circuitry and the cerebellar vermis. Latest studies have examined an interaction effect between genetics, neuronal pathways and environmental factors as precursors to ADHD symptoms. Some theories suggest that the environment (both positive and negative) could influence certain genetic risk factors for ADHD. About a genetic-environmental interaction, perhaps risk factors such as maternal smoking may alter base pairs within the DNA pathway, which may correlate with symptoms of ADHD. Research suggesting a genetic-environmental interaction will be analyzed and reviewed. This systematic review will describe some of the most current studies, critique their methodology and analyzes, and offer ideas for future research.

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Methods

The authors selected representative studies from Germany, Iran, Italy, The Netherlands, Sweden, United Kingdom, and the United States from the year 1992 to 2014. All studies were published in scientific journals, books, or research from the National Institute of Health. 60 articles were reviewed, and at least 20 were used in this review. These studies were chosen because they represented the topic of interest, risk factors and ADHD, the most advanced research of the day, and gave us a window into the possibilities for research hypotheses in the future.

Data search was performed in June of 2014. Databases used were Pro Quest Psychology Journals, Medline, and Psych Info.

Smoking: Risk factors

Reviewing risk factors for hyperactive-impulsive symptom severity in ADHD, such as socioeconomic status, psychiatric disorders in the family, alcohol consumption during pregnancy, birth weight, and smoking during pregnancy, researchers found only smoking during pregnancy was associated with hyperactive-impulsive symptoms ($P < 0.050$). Maternal prenatal smoking is a risk factor co-morbid with conduct disorder and ADHD.[4] Freitag et al., found family risk factors increased symptoms of inattention but not hyperactive-impulsive symptoms.[4]

A limitation of the study was that for certain data, a general classification regarding ongoing parental smoking during infancy and childhood was delineated. In other words, that category was imprecise. In addition, there was no control group.

Smoking and DAT1

Previous research on maternal prenatal smoking looked at children from birth to early adulthood. Researchers demonstrated that children homozygous for the 10 repeat (r) allele of the common DAT1 polymorphism whose mothers smoked before the infant's birth, exhibited significantly higher hyperactivity-impulsivity scores than children without these environmental or genetic risks.[5] Therefore, children with the 10 repeat allele of DAT1 were associated with precursors of ADHD. Researchers found a significant interaction between the DAT1 genotype and maternal prenatal smoke exposure, using an interaction regression coefficient of DAT1 +/+ x prenatal smoking, significant with a P value of $P = 0.012$. This finding indicated that males with prenatal smoke exposure homozygous for the DAT1 10 r allele had higher hyperactivity symptoms as compared to males from all other groups. In females, no significant main effects of DAT1 genotype, nor prenatal smoke exposure, nor interaction effects on any symptoms, were evident at ($P > 0.250$).[5] Although the authors indicated this was a prospective longitudinal study from the child's birth to early adulthood, maternal prenatal smoking was actually determined retrospectively, when the infant was 3 months old. Additional limitations were that adolescents were used in the sample. This was an important limitation because symptoms and prevalence of ADHD are reported to change substantially from childhood to adolescence. Another limitation was exclusively using the symptoms of ADHD and oppositional conduct disorder, instead of the DSM-IV diagnosis from the diagnostic manual. The researchers said this was done because too few children filled the diagnostic criteria.

Smoking and alcohol

Prenatal exposure to nicotine and or alcohol has been suggested to increase the risk of ADHD. A female twin study gathered and analyzed telephone interview data from parents of female twin adolescents born during 1975-1985. This study looked at 1091 pairs of monozygotic twins and 845 pairs of dizygotic twins.[6] Statistical models were used to determine relative contributions of parental smoking and drinking alcohol during and after pregnancy, as risk factors for DSM-IV, ADHD.

Findings showed ADHD was more likely to be diagnosed in girls whose mothers were alcohol abusive/dependent during pregnancy with an adjusted odds ratio (OR) of 1.73, $P < 0.050$. (Adjusted OR is a more

conservative estimation). Fathers who were alcohol dependent had an OR of 2.00, which was significant for ADHD at the P < 0.010. Mothers who reported heavy alcohol use during pregnancy and gave birth to infants with low birth weight were more likely to have children who were later diagnosed with ADHD. For infants who had low birth weight, the OR was 1.86, significant at the P < 0.010 level. Controlling for other risk factors, risk for ADHD in female children, was not significantly increased in those whose mothers smoked during pregnancy. Looking at the effects of prenatal childhood predictions, 86% of the residual variance in ADHD was attributable to genetic effects and 14% was attributable to non-shared environmental influences. The researchers concluded that the prenatal and parental risk factors may not be important mediators influencing the risk for ADHD in female children because much of the association between these variables and ADHD appear to be indirect.

One limitation of this study was that it was a retrospective study, regarding risk of smoking and alcohol risk problems with ADHD. Other limitations included that only the mothers were asked questions about smoking and drinking alcohol during pregnancy. Their answers were not corroborated by any other measures. Therefore, there could be recall bias. Additionally, the category of birth weight was "anything < 1700 g or 3.75 pounds." Birth weight was not established by low or very low categories. Furthermore, confidence intervals for smoking variables were broad. Thus possible important effects could not be excluded in this sample. Furthermore, the Wald test was a poor choice for a study with a large sample size. For a small sample size, it is a good estimation.

Prenatal exposure to nicotine has been more consistently associated with conduct problems and delinquency in males.[7] In some of these studies, other measures were not addressed, such as pre and perinatal influences of family adversity (severe marital discord),[8] traumatic brain injuries,[9] and severe deprivation.[10] All of these measures were found to be associated with ADHD in childhood.

Previous maternal history of medical disorders

Malek et al., performed a case-control study of 164 children with ADHD and 166 children who were controls, selected randomly from primary and guidance schools in Iran. Both groups were compared with previous medical history of diseases in children and parents. The frequency of maternal history of medical disorders (28.7% vs. 12.0%; P = 0.001) was significantly higher in children with ADHD when compared to the control group, using the Fisher's exact test and logistic regression model.[11] Maternal history of medical disorders in parents of ADHD children using a chi-square was $\chi^2 = 1.06$, P < 0.010. Malek et al., asked about numerous diseases and disorders pertaining to children with ADHD and their parents. One disorder they asked the parents about was head trauma to the child. Although they asked about the history of the type of head trauma in children with ADHD, the exact severity of head trauma was unclear. Perhaps, future studies could include classifications of types and severity of head trauma as a precursor of ADHD.[11]

Preterm birth

Moderate preterm birth

Perricone et al. researched 50 moderately pretermed birth children (34.6 weeks) and 50 controls (40 weeks) in an Italian preschool. The researchers' aim was to study the presence or lack of precursors of ADHD in moderately preterm children in comparison to full term children. Using a type of factorial MANCOVA, results on the teacher checklist indicate there were significant effects of gender and moderately preterm children on inattention $F_{(1,99)} = 3.3$, P = 0.040.[12]

The parents' checklist found a significant difference related to preterm birth and hyperactivity and impulsivity, $F_{(1,99)} = 1.14$, P = 0.046 and inattention, $F_{(1,99)} = 7.8$, P = 0.048. Preterm children obtained higher scores in comparison to full term children. Therefore, the number of children

moderately born preterm, characterized by precursors of hyperactivity appear statistically higher than in the group of children born full term (χ^2 = 17.7, df = 2, P = 0.001). Although this study was retrospective about the questions asked the children and mothers regarding the birth of the child, the answers were corroborated with medical and birth records of the children.[12]

Extreme preterm birth and social adversity

Lindstrom et al. researched extreme preterm birth, moderate preterm birth, and increases in children having ADHD using the degree of immaturity at birth. Social adversity, as expressed by low maternal education was also reviewed to see whether it modifies the risk of ADHD in preterm birth. A total of 1180616 subjects were included in the study. Included were children born between 1987 and 2000 and followed up for ADHD medication in 2006. The childrens' age ranged from 6 to 19 years.[13] The researchers performed a logistic regression of ADHD medication and gestational age. Findings were that at the gestational age of 23-26 weeks (extreme preterm birth); looking at year of birth, gender and county of residence in Sweden, 2.5 (1.8-3.5) with an OR of 95% confidence level, had the highest number of prescriptions for ADHD medication. ADHD medication was more common in the presence of the following: Teenage mother, single parent, public welfare, low maternal education, maternal as well as paternal addictive/psychiatric disorder, low gestational age, small for gestational age, low Apgar score, maternal smoking during pregnancy, and cerebral palsy.

It is important to note that a refinement of cortical connection peaks at gestational weeks 27-28 and the number of neurons around week 28.[14] This fact may suggest a reason for evidence of a maturational lag in children with ADHD.[15] That is; the cortical connection may be compromised due to both mother's smoking while pregnant and not having proper medical care during pregnancy.

Genetic-environmental interaction

Current theories in ADHD show evidence supporting multiple genetic and environmental factors that interact during early developmental stages in the fetus to create a neurobiological susceptibility to ADHD.[16]

Some researchers believe that the expression of ADHD is mediated by alterations within different neural networks and pathways and the deficits created in the neuropsychological functions they serve. ADHD symptoms create difficulties in the domains of attention and cognitive functions: Problem solving, planning, sustained attention, response inhibition and working memory. Neuroimaging and magnetic resonance imaging (MRIs) are helpful in showing strong evidence of the frontostriatal network as a likely contributor to the pathophysiology of ADHD. Reductions in volume have also been observed in the total cerebral volume including the pre-frontal cortex, the basal ganglia, the dorsal anterior cingulate cortex, the corpus callosum and the cerebellum.[17]

Gray matter and white matter

In studies of cortical development in children with ADHD, A delay in brain maturation was seen: The gray matter could peak approximately 3 years later than in healthy controls.[18] This delay is most prominent in the pre-frontal regions controlling attention and motor planning.[18,19]

Diffusion tensor imaging (DTI) is an MRI modality that provides information about direction and integrity of neural fiber tracts in the brain in vivo. DTI studies have revealed developmental changes in cortical white matter pathways in the prefrontal regions of the brain and the pathways surrounding the basal ganglia and cerebellum in patients with ADHD. It is believed that these changes cause a decrease in the speed of neuronal communication.[20] Researchers believe these changes are caused by decreasing myelination of axons. The neural networks serving the corticostriatal and cortico cerebellar circuits could represent biomarkers for ADHD.

Genes-genetic influence on behaviors and cognitive outcome in favorable environments

DAT, DAT1 Gene and ADHD

DAT1 has been implicated in ADHD although the mechanism by which it exerts its effects remains unknown. DAT1 are predominately expressed in the striatum but also in the cerebellar vermis. Durston et al.[21] investigated the DAT1 gene effects on brain activation patterns in all male sample of sibling pairs discordant for ADHD (n = 20) and controls (n = 9).

The subjects participated in a functional MRI session using a go/ no-go paradigm using Pokemon characters. A DNA sample was obtained from each subject. Activation in the striatum was greater for the carriers of the 9 r allele ($t = 3.93$, $df = 28$; $P < 0.001$) Whereas activation in the vermis of the cerebellum was significantly greater for individuals homozygous for the 10 r allele ($t = 4.10$, $df= 28$; $P < 0.001$).[21]

Limitations of this study include the very small sample size, the assessments conducted in Dutch language may have a cultural bias when compared with other cultures, and 5 out of 10 subjects with ADHD were taking stimulant medication prior to the study. All subjects discontinued their medication for at least 24 h prior to the scan, but this period may not have been long enough to eliminate the medication from their system. Finally, the task using Pokemon characters may be more appealing and may have affected activation patterns in the brain more than if the task characters were different.

Positron emission tomography studies have shown that methylphenidate hydrochloride (MPH) (Ritalin) blocks DAT and that extracellular dopamine (DA) increases in proportion to the level of blockade and to the rate of DA release. This process is associated with enhanced perception of external stimuli, which is very important with subjects who have ADHD.[16] This fact may explain the improvements in sustained attention and improved performance in children with ADHD, when prescribed MPH.[22]

LPHN3

Two genes (LPHN3and 11Q) have gained attention due to a large sample of multi-generational families studied in Colombia.[23] (In the 11Q, a portion of chromosome 11 is missing or deleted.) Research investigation led to identifying the LPHN3 gene, a member of the lactrophilin subfamily of G-protein-coupled receptors involved in GABA-ergic neurotransmission. A common LPHN3 haplotype (a group of genes inherited together by an organism from a single parent) was associated with ADHD susceptibility and with its response to stimulant medication. The interaction between LPHN3 and 11Q doubles the risk of ADHD and predicts severity and outcome.[24,25] Evidence also suggests that LPHN3 is involved in brain development with emerging ADHD.[26]

Choudhry et al. examined the association between single nucleotide polymorphisms (SNPs) in LPHN3.[27] (SNPs are the most common type of genetic variation among people). The family-based association test (FBAT) was conducted on 380 families with ADHD. Their response to treatment was measured when given a fixed dose of methylphenidate 0.5 mg/day. A stratified FBAT analysis of maternal smoking and stress during pregnancy was conducted.

The stratified analysis, based on maternal stress during pregnancy found a highly significant association observed in the no stress group with LPHN3 and ADHD behaviors on the child behavioral checklist, ranging from $P < 0.050$ to $P < 0.001$. In contrast, a complete lack of association was noted in the "stressed" group (moderate to severe). The researchers looked at the association between four tag SNPs and the diagnosis of ADHD. Behavioral and cognitive traits of ADHD, as well as treatment response, were highly significant in the group where mothers experienced mild or minimal stress during pregnancy. Limitations of this study were the very small sample size, the possibility of a Type II error (false negative) in the children exposed to maternal stress, and the retrospective nature of the study. Furthermore, if the mother smoked at any point during the study, the

child was coded as "exposed." Consequently, smoking was not precisely measured.

Discussion

Considering the limitations of the previous studies, there continues to be much that can be researched and learned about ADHD in the future. Perhaps, certain genes are linked to low stress in the womb and in different stages of childhood and have positive outcomes. How these genes are affected, may determine whether or not a child experiences ADHD symptoms and to what severity. Depending on the affected genes and the sex of the child, a particular child may not exhibit the same ADHD symptoms due to differences within the X and Y-chromosomes. Smoking or other stressors may have an effect on chromosomes or even the expression of genes within these chromosomes, perhaps making male children more susceptible since they have only one X chromosome whereas female children have both X chromosomes and form a barr body. This may explain the reason that female children tend to experience the inattentive type of ADHD more often and the hyperactivity type, less often, than male children. Other genes, when linked to high stress in the womb and in different stages of childhood, are correlated with hyperactivity-impulsivity and conduct disorder.

Many findings are difficult to interpret because genetic and phenotypic heterogeneity increases as quickly as new genes associated with ADHD are discovered.[24] Furthermore, the potential presence of non-linear interactions between genes has been insufficiently explored, since the number of possible gene interactions increase exponentially as a function of the number of loci (Slatkin).[28] When Arcos-Burgos and Muenke, reviewed a sample from Norway and controlled the effect of LPHN3 on ADHD, they found a reduction of approximately 9% in the prevalence of ADHD in the Norwegian population. Therefore, these researchers conclude that certain statements in psychiatric genetics have been greatly exaggerated.[23]

Factors due to drinking or smoking while pregnant can affect the nervous system, which later may be linked to ADHD symptoms because they may alter genes during development by causing a genetic variation. Smoking or drinking may cause damage to developing frontostriato-circuitry or the cerebellar vermis, which may later manifest some ADHD symptoms in children.

Researchers have speculated that ADHD and autism spectrum disorder may originate in similar parts of the brain. More technological advances in imaging and in genetic-environmental interactions are necessary to determine the origin of both disorders.

One potential toxin, nicotine, can act on nicotinic receptors in the brain, in the same way, that acetylcholine does. Acetylcholine acts on nicotinic receptors by causing excitation of the ganglionic neuron or muscle fiber, which may account for some ADHD symptoms. Nicotine poisoning can reflect widespread autonomic activation.[29] Perhaps these effects may be more prominent in the developing fetus and may account for the maturational lag experienced by children affected with ADHD. Future studies could determine nicotine levels during early pregnancy within the fetus. Perhaps, a blood test could be analyzed whenever an amniocentesis is performed during 16-22 weeks of pregnancy, to determine the amount of nicotine in the fetus.

Conclusion

Future research could benefit from using prospective, longitudinal studies, with large sample sizes. For genetic-environmental studies, the DNA of the pregnant mother, a father and infant, (after birth) could be taken, before and during the research. Blood samples from both parents could also be analyzed as well as measuring stress levels of the parents and children.

Many studies did not look at potential DNA defects, stressors, etc., from the father. Could men be passing some susceptibility factor for ADHD on the Y chromosome that

female children do not experience when the mother smokes during her pregnancy?

Future research could also look at monozygotic twins separated at birth and from their biological parents to glean clear differences between genetic and environmental factors of precursors of ADHD. Although adoption studies could provide more information about environmental factors, some complicating issues remain. Adoption agencies prefer not to separate twins from their sibling. Furthermore, adoption itself, may frequently cause issues of anxiety, abandonment and anger in the adopted child. Symptoms of anxiety may need to be measured because anxiety may contribute to the symptoms of inattentive ADHD while anxiety, anger and abandonment may contribute to the severity of ADHD and co-morbidity with conduct disorder.

With contradictory results and many competing theories about precursors of ADHD, more research will need to be performed in the future. More advanced genetic technology will help researchers in learning more about ADHD's complex risks, precursors, and symptoms.

Conflict of Interests

Authors have no conflict of interest.

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