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Review article

Exposure to neurotoxicants and the development of attention deficit hyperactivity disorder and its related behaviors in childhood ☆

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ABSTRACT

The purpose of this manuscript is to review the literature to determine evidence of associations between exposure to prenatal and postnatal environmental agents and the development of attention deficit hyperactivity disorder (ADHD) and related behaviors. A review of published research literature was conducted on associations between exposures to prenatal and postnatal cigarette smoke, prenatal exposure to alcohol, cocaine, and heroin, childhood exposure to lead, and prenatal exposure to organophosphate pesticides and outcomes of ADHD or behaviors related to ADHD.

Review of the literature in these areas provides some evidence of associations between each of the exposures and ADHD-related behaviors, with the strongest evidence from prenatal cigarette and alcohol exposure and postnatal lead exposure. However, research on each exposure also produced evidence of weaknesses in these hypothesized links due to imprecise research methodologies and issues of confounding and inaccurate covariate adjustment. More rigorous studies are needed to provide definitive evidence of associations between each of these prenatal or postnatal exposures and the development of ADHD or symptoms of ADHD.

Future studies need to clarify the underlying mechanisms between these exposures and the increased risk for ADHD and associated behaviors. More research is also needed utilizing study designs that include genetic information, as ADHD is highly heritable and there appear to be some protective mechanisms offered by certain genetic characteristics as evidenced in gene by environmental studies. Finally, while studies focusing on individual drugs and chemicals are an important first step, we cannot ignore the fact that children are exposed to combinations of drugs and chemicals, which can interact in complex ways with each other, as well as with the child's genetic makeup and psychosocial environment to influence ADHD risk.

Contents

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; CPT, continuous performance task; DSM, Diagnostic and Statistical Manual of the American Psychiatric Association; FAS, fetal alcohol syndrome; KSADS, Kiddie-Schedule for Affective Disorders and Schizophrenia; OP, organophosphate pesticide; OR, odds ratio; PAE, prenatal alcohol exposure; PCE, prenatal cocaine exposure; PCS, prenatal cigarette smoke; SES, socioeconomic status; SHS, second hand smoke.

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common, brain-based, neurodevelopmental, biological condition that first manifests in childhood and is associated with significant comorbid pathology and functional impairments across the lifespan. Clinical descriptions of the syndrome now known as ADHD have been documented in the medical literature at least since the early 20th century. Various names have been given over the years, including minimal brain damage, hyperkinesis, and attention deficit disorder (ADD). As currently defined by the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-V) (American Psychiatric Association, 2013), ADHD is diagnosed in the presence of developmentally inappropriate levels of inattentive and/or hyperactive impulsive symptoms that have been present since childhood, have persisted for at least 6 months, cause clinically significant difficulties in multiple areas of life, and are not better accounted for by another mental or behavioral disorder. Recent changes to DSM ADHD criteria include adjusting the required age of onset from 7 to 12 years for some symptoms, improving the developmental sensitivity of criteria by reducing the number of symptoms required for diagnosis in individuals ages 17 and older, and eliminating the diagnostic exclusion of individuals with other disorders.

ADHD is the most common behavioral disorder of childhood, with worldwide prevalence estimates ranging from 3% to 9% of school-age youth (Faraone et al., 2003; Froehlich et al., 2007). More recent studies have reported an estimated U.S. prevalence in children of 9.4% (Visser et al., 2010) to 10.6% (Wolraich et al., 2012). The National Comorbidity Study Replication found a 4.4% prevalence among U.S. adults (Kessler et al., 2006). ADHD is a significant risk factor for co-occurring psychiatric disorders, including other disruptive behaviors, mood and anxiety disorders, antisocial activities, and substance abuse and dependency (McGough et al., 2005; Pliszka, 1998). Adults with ADHD have significantly higher rates of academic underachievement, unstable personal relationships, employment problems, poor health choices, driving accidents, and decreased income compared to those without ADHD (Barkley, 2002; Biederman et al., 2006). Thus, ADHD has been identified as a significant and growing public health concern.

The heritability of ADHD, based on twin and adoption studies, is estimated at 75% (Faraone et al., 2005). Nonetheless, identification of a specific gene or genes that are causative has remained elusive. After great initial interest in candidate gene studies, researchers acknowledged that numerous candidates predicted only small increases in ADHD (Faraone et al., 2005). Genome wide association studies similarly failed to identify areas of significant risk (Neale et al., 2010). Recently, it has been recognized that individuals with ADHD have greater frequencies of rare mutations, or copy number variants, throughout their genomes, but these are not specific to the disorder (Thapar et al., 2010). Several interesting small studies have demonstrated a moderating effect of certain genetic variants on environmental risks (Ficks and Waldman, 2009). At present, ADHD is best conceptualized as a complex trait that arises from the interplay of numerous genetic, environmental, and developmental factors (Faraone et al., 2005).

The purpose of this manuscript is to review the current literature on exposures to environmental toxicants and drugs of abuse that have been linked with the development of ADHD in childhood. A definitive diagnosis of ADHD typically requires assessment by a medical professional with specific training in child behavior. However, due to cost and feasibility issues, many research studies rely on assessments of child behaviors that are characteristic of ADHD rather than requiring a medical diagnosis. In our review, we have included both types of studies; those that have provided an ADHD diagnosis and those that have assessed externalizing, attention, and impulsivity behaviors that are often associated with ADHD. The exposures of interest are most likely to occur in the uterine environment during gestation, but some may also occur in the postnatal period during infancy and/or early childhood. We review the evidence linking the following pre- and/or post-natal exposures with ADHD or its related behavioral characteristics: cigarette smoke; alcohol; cocaine and opiates; lead; and organophosphate pesticides. It is important to note that the amount of evidence linking these exposures to ADHD and ADHD-like behaviors is somewhat imbalanced among these various exposures. For example, research linking prenatal cigarette smoke (PCS) and prenatal alcohol exposure (PAE) to ADHD is better developed than research on organophosphate pesticides for which cohort studies are just now examining childhood outcomes. There are three main areas we have chosen not to include in this review. While the animal literature adds an additional layer of evidence linking exposure to behavioral outcomes, we have focused on research in humans; animal research is beyond the scope of this review. In addition, while neuroimaging studies have begun to provide evidence of correlated structural and functional brain changes that may occur with environmental exposures and among children with ADHD, a review of that literature that should be conducted by experts in the field of neuroimaging. Lastly, we have not included studies of behavioral outcomes in infancy as links to later ADHD symptomatology have not been clearly established.

2. Tobacco

2.1. Prenatal exposure

Cigarette smoking is the leading cause of preventable morbidity and mortality in humans (CDC, 2010), yet tobacco is the most commonly