

Teratogenic Effect of Alcohol on Brain and Behavior

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Abstract: Heavy alcohol exposure can have serious and long-lasting effects on the developing fetal brain. In the last decade, researchers have utilized quantitative structural magnetic resonance imaging (MRI) to examine the brains of living children and adults with histories of heavy prenatal alcohol exposure. In addition to microcephaly, these studies indicated structural abnormalities in various regions of the brain, including the cerebellum, corpus callosum, and the basal ganglia. Most recently, we have utilized novel imaging and analytic techniques to study the brain as a whole in an effort to elucidate more subtle differences than was possible with earlier techniques. Results indicated displacements in the corpus callosum, increased gray matter densities in both hemispheres in the perisylvian regions, and altered gray matter asymmetry in portions of the temporal lobes in the brains of alcohol-exposed subjects. In addition, prominent shape abnormalities were observed in the brains of these subjects, with narrowing in the temporal region and reduced brain growth in portions of the frontal lobe. These results imply that brain growth continues to be adversely affected long after the prenatal insult and that the brain regions most affected may be consistent with the neurocognitive deficits characteristic of individuals prenatally exposed to alcohol. (1) FAS is defined by four criteria: maternal drinking during pregnancy; a characteristic pattern of facial abnormalities; growth retardation; and brain damage, which often is manifested by intellectual difficulties or behavioral problems. (2)

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1. Introduction

The Claim that drinking alcoholic beverages during pregnancy can affect the offspring development has a long history. Little attention was given to this problem until about 20 years ago. Clinicians in France published the first report suggesting that prenatal exposure to alcohol could damage the developing fetus. A little years later Jones and his associate in Seattle published similar findings. Neither the scientific literature nor the surgeons general warning advising that women should abstain from drinking alcohol during pregnancy has prevented pregnant women from consuming alcohol. As a result maternal alcohol abuse remains a leading known cause of mental retardation in western world. (3)

2. Results from Neuropsychological Studies

Generally, heavy prenatal alcohol exposure is associated with deficits in a wide range of areas of function, including both cognitive functioning (e. g. , general intellectual functioning, learning of new verbal information, and performance on visual-spatial tasks) and fine-and gross-motor performance. Neuropsychological studies have analyzed the cognitive impairment of children with histories of prenatal alcohol exposure. Although many of these studies have focused on children diagnosed with FAS(fetal alcohol syndrome), several analyses have included children with FAE or PEA. Importantly, many studies show that strong similarities exist between children with FAS and children with FAE(fetal alcohol effect) / PEA(prenatal alcohol exposure)

For example, studies of overall cognitive ability in FAS children typically report average IQ scores in the borderline range of functioning (i. e. , in the low 70s) , although they can range from intellectually deficient (IQ scores less than 70) to average (IQ scores between 90 and 109) . Children with FAE or PEA also show deficits in IQ scores, although

these deficits typically are not as severe as in the children with FAS (4) (5)

In addition to overall intellectual or cognitive deficits, researchers have evaluated a broad range of cognitive functioning areas in children with FAS, FAE, or PEA, including language skills, visual-spatial functioning, fine-motor behavior, nonverbal learning, and academic performance. In general, alcohol-exposed children both with and without FAS show significant impairments in all neuropsychological areas with few qualitative differences observed between the FAS and PEA/ FAE groups. Similarly, high levels of prenatal alcohol exposure are related to an increased risk for cognitive deficits across a range of functioning areas, which again can occur in children both with and without a diagnosis of FAS.[2]

3. Learning and Memory

Both anecdotal information and results from animal studies have indicated that prenatal alcohol exposure can affect learning and memory. Studies of children with FAS generally have supported this observation, although the deficits in memory may not be as global as was once thought. For example, one study investigated verbal learning and memory in children with FAS and in non-alcohol-exposed control children (6) . The study found that although the FAS children demonstrated some deficits in memorizing verbal information, these deficits resulted from difficulties with the acquisition of the information rather than with the ability to remember the information over time. Other studies also have revealed similar deficits in the acquisition of nonverbal information in alcohol-exposed children (7), suggesting that learning deficits occur in both verbal and nonverbal arenas and are likely to cause significant impairment in diverse areas of functioning. It is unclear, however, whether the degree of impairment for each child differs between the verbal and nonverbal areas of function.

Some studies suggest that children with FAS can perform well when memory function is tested in a different way, for example in tests of implicit memory a type of memory that is not under conscious control. When subjects successfully perform implicit memory tests, they may use information from previous tasks without being aware that they have done so. In one study, investigators showed children with FAS lists of words and asked the children to rate those words on likeability (8). (This rating component served to enhance the children's attention to the words.) Later in the testing session, the children were asked to complete partial words (e.g., MO or SM) with the first word that came to mind (e.g., MOUSE or SMILE). The children were not reminded of the previous words nor prompted to remember them by the examiner. Nevertheless, both FAS and control children were more likely to complete the partial words with words from the previous task than with new words. These results indicated that both groups of children used implicit memory and that prior exposure helped them learn and memorize the words. Taken together, these findings suggest that although children with FAS may have significant impairments in learning new information, their overall memory function is complex and may not be as globally affected as was commonly thought. Nevertheless, specific aspects of memory may be affected by prenatal alcohol exposure.

4. Executive Functioning

The term "executive functioning" refers to a group of higher-level cognitive abilities, such as solving problems, thinking abstractly, planning ahead, and being flexible in one's thought processes. These types of skills are independent of overall intellectual function and influence whether and in what manner a person can complete a task. Conversely, tests of other cognitive abilities tend to assess how well, or at what level, a person performs a skill (9). (For more information on executive functioning and the effects of prenatal alcohol exposure on these skills, see the article in this issue by Kodituwakku and colleagues, pp. 192-198)

Children with heavy prenatal alcohol exposure (both with and without FAS) have demonstrated impairments on executive functioning tasks (10). Importantly, in these studies the children's deficits in executive function were unrelated to their overall intellectual levels. This finding is supported by a recent study among adults with FAS or FAE, which found that the subjects' deficits in executive functioning were greater than would have been predicted if they were related to overall IQ scores (11).

Deficits in executive functioning can have real-life implications for people prenatally exposed to alcohol. For example, people with heavy prenatal alcohol exposure may act without first considering the consequences of their behavior or they may have difficulties with activities that require problem solving or with planning a sequence of activities. These types of deficits may explain why children with heavy prenatal alcohol exposure, even those with average IQ scores, have difficulty succeeding in school.

5. Psychosocial Deficits and Problem Behaviors

Studies involving parent reports and interviews have suggested that alcohol-exposed children with or without FAS not only have cognitive deficits but also are at high risk for problem behaviors that can interfere with their participation in home, school, and social environments. For example, these children appear to be at increased risk for psychiatric disorders, trouble with the law, alcohol and other drug abuse, and other maladaptive behaviors (12). Moreover, they are more likely than non-alcohol-exposed children to be rated as hyperactive, disruptive, impulsive, or delinquent (13). Similarly, on measures of adaptive ability and skills necessary to perform age-appropriate daily living activities, adolescents and adults with FAS often exhibit poor socialization and communication skills. In addition, the majority of these adolescents and adults display significant maladaptive behaviors (e.g., impulsivity) and are less likely to be living independently (14). It is noteworthy that these problems occur in people prenatally exposed to alcohol whether or not they meet the criteria of FAS and occur to a greater extent than would be predicted by the person's general intellectual functioning or demographic factors.

6. Results from Brain Imaging Studies

The neuropsychological and behavioral deficits described in the previous section represent real-life manifestations of the effects of prenatal alcohol exposure. Although deficits on these measures are thought to provide evidence of underlying changes in brain structure or function, they represent only indirect measures of such brain changes. Alcohol's direct effects on brain development were already noted in the earliest reports of FAS (15), however, and autopsy studies of brains from people with FAS noted numerous and wide-spread brain abnormalities. Because these cases represented only the most severely affected children, it is problematic to generalize the findings to all people living with FAS. With the advent of numerous structural imaging techniques, such as magnetic resonance imaging (MRI), and functional imaging techniques, such as electroencephalography (EEG), positron emission tomography (PET), and single photon emission computed tomography (SPECT), however, researchers can now study the living brains of alcohol-affected children in a relatively noninvasive fashion.

7. Potential Causal Mechanisms

The mechanisms that underlie alcohol-induced fetal brain damage have been studied in experimental animals and in nerve cells (i.e., neurons) grown in culture (16). Within the fetus, embryonic cells destined to become brain neurons grow in number, move to their ultimate locations, and mature into a wide variety of functionally distinct neuronal cell types, eventually forming connections with other brain cells in a predetermined pattern. Alcohol metabolism is associated with increased susceptibility to cell damage caused by potentially harmful substances called free radicals. Free radical damage can kill sensitive populations of brain cells at critical times of development in the first

trimester of pregnancy (17) (18). Other animal experiments suggest that the third trimester may also represent a particularly sensitive period for brain cell damage associated with FAS (19).

Alcohol or its metabolic breakdown products can also interfere with brain development by altering the production or function of natural regulatory substances that help promote the orderly growth and differentiation of neurons (17). Research using animals or cell cultures show that many of alcohol's adverse effects on brain cells can be prevented by treatments aimed at restoring the balance of regulatory substances upset by alcohol (20) (21). Promising results have also been obtained in similar experiments by administering substances (i.e., antioxidants) that help protect cells against free radical-induced cell damage (22). This is only one of several potential mechanisms that may contribute to alcohol-related fetal injury. Further research is needed to determine if such an approach might prove both effective and safe in humans during pregnancy.

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