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The Influence of FASD on Psychiatric Disorders: A Literature Review on the Mechanisms Relating Fetal Alcohol Spectrum Disorders to Mental Health Conditions in Adulthood

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ABSTRACT

Background The Fetal Alcohol Spectrum Disorders (FASD) encompass a variety of physical, behavioral and neurological disorders resulting from fetal alcohol exposure. FASD includes full Fetal Alcohol Syndrome (FAS), partial FAS (pFAS), Alcohol-Related Neurodevelopmental Disorder (ARND) and Alcohol-Related Birth Defects (ARBD). It is estimated that there is an average of 7.7 cases per 1000 people worldwide. Despite its frequent occurrence, FASD is often underdiagnosed what results in affected patients do not receive appropriate assistance and care that would mitigate its negative effects. Alcohol is a toxic substance for the developing fetus, and its impact depends on factors such as the amount of alcohol consumed, the timing of exposure, and individual genetic predispositions.

Aim of the study This paper analyzes the neurobiological, epigenetic and environmental mechanisms underlying the relationship between FASD and the increased risk of psychiatric disorders, such as depression, anxiety disorders, ADHD, addictions and adjustment disorders. The critical role of dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, chronic inflammation in the central nervous system and epigenetic changes affecting the expression of genes related to brain development is emphasized. The study also discusses diagnostic difficulties arising from the lack of definitive tests and highlights the importance of early diagnosis and interdisciplinary therapeutic care in minimizing the long-term effects of FASD.

Material and methods Literature available in the PubMed database was reviewed using the following keywords:
“FAS”, “FASD”, “Fetal Alcohol Spectrum Disorder”, “Fetal Alcohol Syndrome”, “alcohol use during pregancy”, “mental disorders in FAS”, “mental disorders in FASD”, “fetal alcohol exposure”, “psychiatric diseases”

Conclusions Fetal Alcohol Spectrum Disorder (FASD) is a significant and preventable cause of birth defects and developmental disorders. The multifactorial mechanisms linking FASD with psychiatric disorders include neurobiological damage, chronic neuroinflammation, and environmental influences. This article highlights the urgent need for global prevention programs and education on the harmful effects of alcohol consumption during pregnancy. It

also suggests further research into epigenetic and neuroprotective therapies to reduce the risk of psychiatric disorders in individuals affected by FASD.

Keywords “FAS”, “FASD”, “Fetal Alcohol Spectrum Disorder”, “Fetal Alcohol Syndrome”, “mental disorders in FAS”, “mental disorders in FASD” “FASD mechanisms”

INTRODUCTION

Fetal Alcohol Spectrum Disorder (FASD) is a term describing various physical, behavioral and neurological disorders resulting from prenatal alcohol exposure (PAE). [1] It was described initially in case reports by Lemoine in 1968 and Jones and Smith in 1973.[2] FASD includes full-blown Fetal Alcohol Syndrome (FAS), partial FAS (pFAS), Alcohol-Related Neurodevelopmental Disorders (ARND), and Alcohol-Related Birth Defects (ARBD).[3] According to global data, FASD affects an average of 7 per 1,000 individuals,[4] with the highest prevalence in Europe (19.8 per 1,000) and in countries with high alcohol consumption, such as South Africa and Ireland. FASD is common but underdiagnosed. It is estimated that globally, between 1,726 and 17,810 new cases of FASD occur every day. [5]

Alcohol is a teratogen, [6] meaning it can disrupt fetal development. Its harmful effects depend on the dose, drinking pattern, duration of exposure and genetic and epigenetic factors of both the mother and the fetus.[7] Alcohol freely crosses the placenta,[8] reaching concentrations in the fetal blood similar to those in the maternal blood, potentially causing damage to all developing organ systems, particularly the nervous system. [9]

Diagnostics Criteria

Diagnosing FASD is challenging[10]. It must always be a diagnosis of exclusion.[11] There is a lack of definitive diagnostic tests.[12] It requires the evaluation of both physical dysmorphic features and nervous system dysfunction.[13] Several diagnostic systems are commonly used, including:

- The CoFASP System (Collaboration on FASD Prevalence),
- The 4-Digit Diagnostic Code from the University of Washington,
- Canadian Diagnostic Guidelines, which have also been adapted in Australia and the United Kingdom.

All three diagnostic systems aim to improve precision in identifying FASD and enable early intervention. The CoFASP system focuses on international standardization and epidemiology, the University of Washington's 4-Digit Diagnostic Code provides detailed clinical analysis, while the Canadian Guidelines promote a multidisciplinary diagnostic approach adaptable to various cultural contexts.

Diagnosis primarily considers confirmation of alcohol exposure during pregnancy.[14] Attention is given to the presence of so-called sentinel features, such as a thin upper lip, smooth philtrum, and short palpebral fissures.[15] In individuals affected by FASD, less characteristic features which may have different etiologies are also observed. For example, low birth weight in children may result from maternal tobacco use during pregnancy. (16) However, FASD is also associated with prenatal and postnatal growth restriction, manifesting as low birth weight and slower weight and height gains during childhood.
Furthermore, individuals with FASD often exhibit structural brain abnormalities (e.g., microcephaly), functional issues (e.g., learning difficulties, memory problems) or lower IQ scores. [17]

The Mental Health Consequences of FASD

Fetal Alcohol Spectrum Disorder (FASD) is associated with a wide range of neurological, cognitive, and behavioral disorders that can persist throughout a person's lifetime. These include memory and learning problems, attention deficits and hyperactivity (ADHD), difficulties in regulating emotions and behavior and an increased risk of psychiatric disorders and addictions later in life. Neurodevelopmental disorders such as ADHD, autism, schizophrenia, and obsessive-compulsive disorder have a complex etiology involving interactions between genetic and environmental factors during fetal development. [18]

Individuals with FASD often face mental health challenges, which may include:

1. Mood and Anxiety Disorders

   Research indicates a high prevalence of depression and anxiety disorders among individuals with FASD. These disorders may result from damage to the nervous system caused by prenatal alcohol exposure, as well as from adaptive and social difficulties stemming from cognitive and emotional deficits.
2. Attention Deficit Hyperactivity Disorder (ADHD) [19]

   ADHD is very commonly diagnosed in individuals with FASD and is one of the most frequently co-occurring psychiatric disorders. These symptoms persist into adulthood and significantly impact functioning in the workplace and social life.
3. Behavioral and Impulse Control Disorders

   Individuals with FASD often struggle with impulse control, leading to risky behaviors, including criminal activities. Increased impulsivity is one of the key factors elevating the risk of involvement with the justice system.
4. Adaptive Disorders

   Difficulties with social and emotional adaptation can lead to chronic stress, exacerbating mental health disorders. Individuals with FASD frequently experience challenges in forming and maintaining relationships, which fosters social isolation and worsens mental health outcomes.

Prenatal alcohol exposure causes changes in the brain's reward and emotion regulation systems, which may increase vulnerability to addictions later in life:

1. Alcohol Addiction

   Individuals with FASD are at higher risk of developing alcohol addiction. Studies show that brain damage, particularly in areas responsible for impulse control and emotion regulation, increases the likelihood of using psychoactive substances to relieve tension and cope with stress.
2. Addiction to Other Psychoactive Substances[20]

   In addition to alcohol, individuals with FASD are at risk of addiction to drugs and other psychoactive substances. The mechanisms underlying this phenomenon include dysfunctions in the dopaminergic system and difficulties in coping with negative emotions.

3. Co-occurrence of Addictions and Other Psychiatric Disorders

   Addictions often co-occur with psychiatric disorders such as depression or anxiety. This pattern of comorbidity may stem from the biological effects of prenatal alcohol exposure as well as from challenging life experiences, such as a lack of social support or exposure to trauma.

DISCUSSION

Mechanisms Underlying the Development of Postnatal Mental Disorders Associated with PAE and FASD

The spectrum of Fetal Alcohol Spectrum Disorders (FASD) is increasingly recognized as one of the most significant potential sources of psychiatric disorders in adulthood.[21] Review articles and empirical studies unequivocally indicate that individuals affected by FASD, particularly those with full-blown Fetal Alcohol Syndrome (FAS), exhibit significantly higher susceptibility to developing various mental disorders, such as anxiety disorders, depression, bipolar disorder, ADHD and substance use disorders. This discussion focuses on the key neurobiological and psychosocial mechanisms that may underlie the increased risk of these disorders in adulthood.

One of the key pathophysiological mechanisms linking prenatal alcohol exposure (PAE) to mental disorders is the hyperreactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Studies indicate that individuals with FASD exhibit elevated cortisol levels in response to stress, which can lead to chronic inflammation in the central nervous system (CNS) and increased susceptibility to anxiety and depressive disorders. HPA axis hyperreactivity may also result in dysfunction of the serotonergic system, which plays a critical role in mood and emotion regulation. [22]

Alcohol interferes with critical signaling pathways essential for brain development. Research shows that disruptions in the Sonic Hedgehog signaling pathway, crucial for brain and craniofacial development, can result not only in the characteristic physical features of FAS but also in brain structural changes, leading to cognitive and behavioral impairments. Additionally, alcohol inhibits the activity of brain-derived neurotrophic factor (BDNF), which is vital for neuronal survival and synaptic connectivity. A deficiency in BDNF leads to impaired neuroplasticity, which can result in learning and memory difficulties, as well as an increased risk of depressive disorders.

Another significant aspect associated with the risk of mental disorders in individuals with FASD is permanent damage to the frontal lobes,[23] responsible for executive functions,

impulse control, and emotional regulation.[24] Deficits in these areas result in decision-making difficulties, impulsivity, and challenges in social adaptation, significantly increasing the risk of behavioral disorders and substance use disorders. Individuals with FASD often face challenging life situations, such as legal conflicts or difficulties in professional life, which further exacerbate the development of secondary mental disorders.

Neurobiological mechanisms associated with chronic neuroinflammation and oxidative stress[25] play a key role in the development of mental disorders in individuals with FASD. Alcohol, by crossing the placenta, activates microglia and astrocytes,[26] leading to chronic inflammation in the CNS. These processes can cause neuronal damage and impaired synaptic plasticity, which are linked to the development of depression, anxiety disorders, and cognitive difficulties in adulthood.

Alcohol causes permanent epigenetic changes, such as DNA methylation[27] and histone acetylation, disrupting the expression of genes responsible for the development and functioning of the nervous system.[28] These changes can lead to long-term neurobiological disorders that manifest as mental disorders, such as depression or anxiety disorders. Importantly, epigenetic changes can be inherited, suggesting the potential risk of intergenerational transmission of susceptibility to mental disorders in populations affected by FASD.

Genetic predispositions to FASD have been demonstrated.[29] Susceptibility to FASD is partially genetically determined, as shown in twin studies and animal models. Genes involved in alcohol metabolism, such as *ADH* and *ALDH*,[30] play a significant role in determining sensitivity to the teratogenic effects of alcohol. [31]

One of the most commonly described problems in adults with FASD is substance use disorders.[32] Damage to the brain's reward system and reduced dopaminergic activity[33] make individuals with FASD more likely to seek substances that artificially stimulate the brain's reward center.[34] Additionally, difficult life circumstances, low social support, and co-occurring mental disorders further increase the risk of substance use as a means of coping with stress and emotional difficulties.

The mechanisms underlying the increased risk of mental disorders and substance use in individuals with FASD are multifactorial. Beyond neurobiological and epigenetic factors, they also include environmental influences. Individuals with FASD often experience social marginalization, which exacerbates stress and increases the risk of mental disorders. A lack of understanding of their problems by their surroundings, as well as insufficient support from the education and healthcare systems, increases the likelihood of secondary disorders. Those

affected by FASD often grow up in environments where violence, addiction, or neglect are present. Early traumatic experiences further intensify the development of anxiety, depressive disorders, and risky behaviors in adulthood. Understanding these mechanisms is crucial for developing effective therapeutic interventions and providing adequate support for individuals affected by this disorder.

CONCLUSION

In conclusion, Fetal Alcohol Spectrum Disorder (FASD) is one of the leading preventable causes of birth defects and developmental disorders. The costs associated with FASD are enormous – in Canada, the annual expenses related to healthcare, education, and the justice system are estimated at 1.8 billion CAD.[35]

The mechanisms underlying the connection between FASD and mental disorders in adulthood are multifactorial, encompassing both neurobiological changes and the influence of environmental factors. Understanding these mechanisms is crucial for developing effective prevention strategies and therapeutic interventions.

Early diagnosis of FASD and the implementation of appropriate interventions are of critical importance, as they can reduce the risk of mental disorders and addictions.[36] Therapeutic programs should focus on building stress management skills, impulse control, and developing social abilities. Given the complexity of health issues faced by individuals with FASD, an interdisciplinary approach to treatment is essential. This should include psychiatry, psychology, addiction therapy, and social and educational support. Implementing support programs for individuals with FASD, such as occupational therapy, educational assistance, and programs aiding in job retention, can help reduce the risk of developing addictions and mental disorders in adulthood. Community support is also vital, including educating families and caregivers to create stable developmental conditions for individuals with FASD. Further research is needed to evaluate the effectiveness of support programs for individuals with FASD and their families, as well as the potential use of epigenetic and neuroprotective therapies to reduce the risk of mental disorders in this population. Preventing the occurrence of FASD also requires public education focusing on the effects and dangers of alcohol consumption by pregnant women.[37]

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