ISSN 1857-9345

HOW ALCOHOL DAMAGES BRAIN DEVELOPMENT IN CHILDREN

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ABSTRACT

The world over, people drink in order to socialize, celebrate, and relax, despite the negative health effects of alcohol. Three periods of dynamic brain changes are evidenced to be particularly sensitive to the harmful effects of alcohol: gestation (from conception to birth), later adolescence (15-19 years), and older adulthood (over 65 years). This article is concentrated only on the negative effects of alcohol in children who have been exposed to alcohol before birth, known as foetal alcohol syndrome (FAS).

This is a review based on published data in PubMed over the last two decades and is an analysis of more than 150 published papers.

Alcohol use during pregnancy can cause miscarriage, stillbirth, and a range of lifelong physical, behavioural, and intellectual disabilities. The effects of ethanol are expressed on a set of molecules involved in neuroinflammation, myelination, neurotransmission, and neuron function.

Modern neuroimaging techniques are able to specify some fine structural changes in the affected areas of the brain: volume reductions in the frontal lobe, including the middle frontal gyri in the prefrontal cortex, hippocampal structure, interhemispheric connectivity, abnormalities in glial cells, white matter deficits etc. Corpus callosum myelination is affected, resulting in a lack of the inter-hemispheric connectivity. This is known to facilitate autism, stroke, schizophrenia, as well as dementia, disrupts cognitive performance, and may lead to neurobehavioral deficits.

It was pointed out that many symptoms and neuroimaging characteristics are similar in ADHD and FAS, thus the anamnesis for prenatal alcohol and nicotine exposure must be taken very seriously in order to better understand and interpret clinical symptoms.

Keywords: foetal alcohol syndrome, neuropsychological characteristics, neuroimaging, modern approach

INTRODUCTION

For thousands of years people worldwide have used fermented grains and fruits to make alcohol. The earliest evidence that humans were brewing alcohol comes from residues in pottery jars found in northern China, dating from 7000 to 6600 B.C. People drink to socialize, celebrate, and relax. Alcohol has a strong effect on people,

but more recently we have begun to struggle with, understand, and manage alcohol's power.

Despite precautions by doctors and medical staff about the risks related to alcohol use, there is no one person in the world who did not consume some form or some quantity of alcohol. What does alcohol cause in healthy adults? Moderate alcohol consumption may provide some health benefits, such as: reducing the risk of developing and dying of heart disease, possibly reducing risk of ischemic stroke and possibly reducing the risk of diabetes. In this context, especially in Mediterranean countries, alcohol is inevitable in the everyday diet.

Researchers in Australia and the UK have shown three periods of dynamic brain changes that may be particularly sensitive to the harmful effects of alcohol: gestation (from conception to birth), later adolescence (15-19 years), and older adulthood (over 65 years) [1].

However, drinking alcohol can cause lifelong physical, mental or behavioural disabilities, especially to unborn children. Globally, around 10% of pregnant women consume alcohol, with the rates considerably higher in European countries than the global average, these facts are alarming.

This article will be concentrated only on the negative effects of alcohol in children who have been exposed to alcohol before birth. Foetal Alcohol Syndrome (FAS) continues to be one of the high-incidence developmental disorders.

Foetal alcohol spectrum disorders (FASDs) are a group of conditions that can occur in a person who was exposed to alcohol before birth. FASD includes several diagnostic conditions: Foetal alcohol syndrome (FAS), Partial foetal alcohol syndrome, Alcohol-related neurodevelopmental disorder (ARND), as well as Alcohol-related birth defect (ARBD) [2].

Alcohol in the mother's blood passes to the baby through the umbilical cord. The safe amount of alcohol during pregnancy is not known. Alcohol can cause problems for a developing baby throughout pregnancy, including before a woman knows she's pregnant. All types of alcohol are equally harmful, including all wines, liquors and beer. It is suggested to avoid alcohol use in the moment of justification of pregnancy (4-6 weeks). Because brain growth takes place throughout pregnancy, stopping alcohol use will improve the baby's health and well-being. Alcohol use during pregnancy can cause a miscarriage, stillbirth, and a range of lifelong physical, behavioural, and intellectual disabilities. These disabilities are known as foetal alcohol spectrum disorders (FASDs) and include physical problems and problems with behaviour and learning. Still, each person with FASD may manifest different symptoms and severity of FASD.

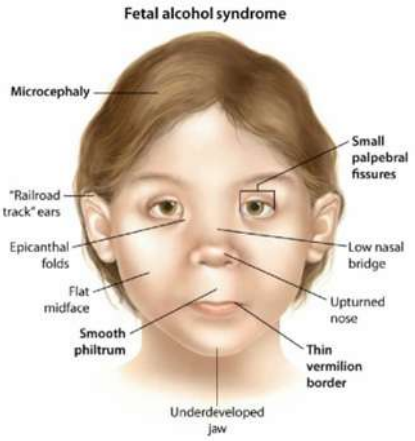

Fig 1. *Main face characteristics in foetal alcohol syndrome*

Children with FASDs might have the following characteristics and behaviours: Abnormal facial features, such as a smooth ridge between the nose and upper lip (this ridge is called the philtrum), small head size (Fig. 1), sleep and sucking problems as a baby, shorter-than-average height, low body weight, poor coordination, hyperactive behaviour, difficulty with attention, poor memory, difficulty in school (especially with math), learning disabilities, speech and language delays, intellectual disability or low IQ, poor reasoning and judgment skills, vision or hearing problems; problems with the heart, kidney, or bones etc. Some studies have argued that the risk of problems depends on the amount consumed, the frequency of consumption, or when during pregnancy the alcohol was consumed. However, experimental data collected from teenage subjects, combined with mathematical modelling, show that there is no safe amount or safe stages during pregnancy for alcohol consumption.

INCIDENCE

The incidence of FAS differs in different regions. It is supposed that 2-5% of people have an FASD, while 2-7 out of 1,000 people have full FAS. In the USA, statistics show that 1 in 20 live births is affected by prenatal alcohol exposure annually,

creating a major public health crisis. Using medical and other records, the CDC (center for disease control) studies have identified 0.2 to 1.5 infants with FAS for every 1,000 live births in certain areas of the United States. The most recent CDC study analysed medical and other records and found FAS in 0.3 out of 1,000 children from 7 to 9 years of age.

Studies using in-person assessment of school-aged children in several U.S. communities report higher estimates of FAS: 6 to 9 out of 1,000 children. Based on the National Institutes of Health-funded community studies using physical examinations, experts estimate that the full range of FASDs in the United States and some Western European countries might number as high as 1 to 5 per 100 school children (or 1% to 5% of the population) [3-7].

While the incidence of FASD is alarmingly high, significant personal and societal costs are the results. Unfortunately, there are no cures for FASD. Alcohol can directly alter the function of neurons in the developing central nervous system (CNS). Unfortunately, during the study in Medicine, very little information is presented regarding the toxic consequences of alcohol for children before birth. Myself, in the 40 years of paediatric practice, I have seen only one baby diagnosed with FAS.

In the following, I will discuss different lesions in the CNS which are proved as a consequences of alcohol use during pregnancies. Data are collected using PubMed articles. More than 150 published articles are analysed.

RESULTS

The teratogenic impact of alcohol on physical growth, neurodevelopment, and behaviour is extensive, and together with clinical disorders falls under the umbrella term of Foetal Alcohol Spectrum Disorders (FASD). Impairments are related mainly to executive function and perceptual learning among affected youth and are linked to disruptions to the growth of the corpus callosum and to myelination in adolescence. However, at least 1 in 10 women will continue to consume alcohol during pregnancy, putting their foetuses at risk for the effects of alcohol exposure [8].

The human brain can be seen as a multi-layered complex network, stimulated by external inputs, to process affective and cognitive information, thus instructing the execution of appropriate responses. In the neurosciences, functional connectivity of neural networks is usually estimated by classical methods, such as correlation and coherence, based on time or frequency domain analysis in sensor space. The exploration of stimulus-activated neural sources and their connectivity provides deep insights into the brain mechanisms of information processing within the complex brain network. Recently, the human somatosensory system has been studied with functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) or electroencephalography (EEG) with tactile sensory stimulation. Results obtained for FAS confirmed a lack of inter-hemispheric connectivity, patterns consistent with previously reported anatomical and neurophysiological measures. This novel method provides feasibility for applying this method to clinical populations to identify biomarkers of disrupted network connectivity that represent the transitions from normal state to disease state, crucial for understanding the mechanism of numerous diseases especially FAS. A lack of inter-hemispheric connectivity is known to facilitate autism, stroke, schizophrenia, as well as dementia, and disrupts cognitive performance. It may also lead to neurobehavioral deficits [9].

Below is a schematic representation of the presented results, published in the journal Chaos (Fig. 2). Subjects who were exposed to alcohol in the womb were more likely to have issues with connections through their corpus callosum, the band of brain tissue that connects the left and right halves of the brain. Deficits in this area have been reported in foetal alcohol syndrome but also, as mentioned before, in people with schizophrenia, multiple sclerosis, autism, depression and abnormalities in sensation.

Alcohol-induced abnormalities in glial cells contribute to the adverse effects of alcohol on the developing brain and have been suspected to do so for a while [10]. A reduction in the cell number and altered development have been reported for several glial cell types in animal models of FAS. In utero alcohol exposure can cause microencephaly when alcohol exposure occurs during the brain's growth spurt, a period characterized by rapid astrocyte proliferation and maturation; since astrocytes are the most abundant cells in the brain, microencephaly may be caused by reduced astrocyte proliferation or survival, as observed in in vitro and in vivo studies.

Children with FAS exhibit hypoplasia of the corpus callosum and anterior commissure, two ar-

eas requiring guidance from glial cells and proper maturation of oligodendrocytes. Additionally, developmental alcohol exposure disrupts microglial function and induces microglial apoptosis. Given the role of microglia in synaptic pruning during brain development, the effects of alcohol on microglia may be involved in the abnormal brain plasticity reported in FASD. The consequences of prenatal alcohol exposure on glial cells, including radial glia and other transient glial structures present in the developing brain, astrocytes, oligodendrocytes and their precursors, and microglia contributes to abnormal neuronal development, reduced neuron survival and disrupted brain architecture and connectivity [11].

A possible scheme for alcohol related alteration in the brain is presented in Fig.3.

In the study of Savage LM.et al (2022) [12] using diffusion tensor imaging (DTI) scanning,

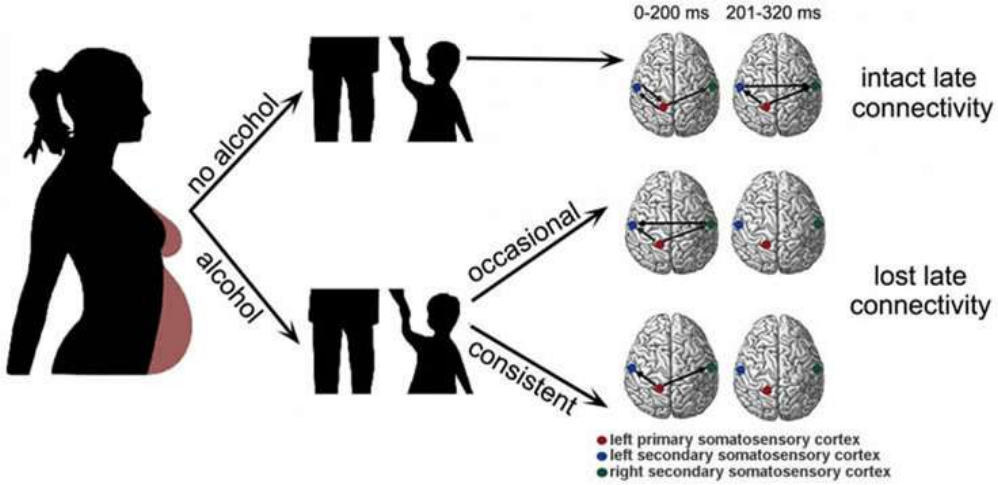

Fig. 2. *The reconstructed networks of the primary (red dot) and secondary (blue and green dots) somatosensory cortex show a lack of inter-hemispheric connectivity in the late response for children prenatally exposed to alcohol (Chaos*. doi:10.1063/1.5089527)

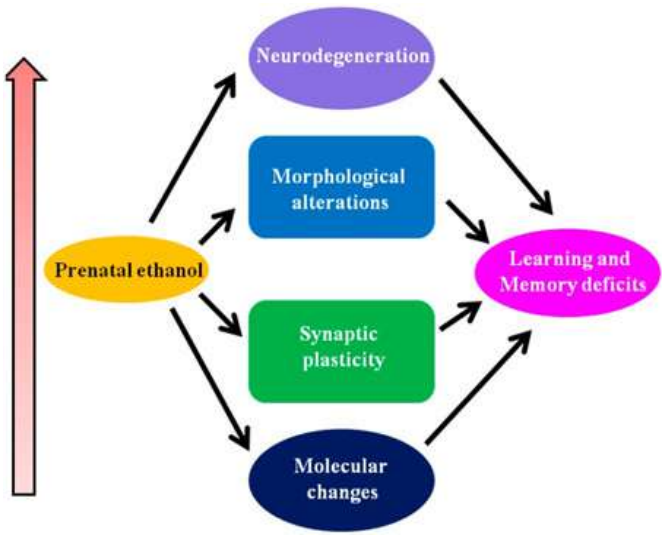

Figure 3. *Prenatal use of alcohol and consequences* (Brain Sci. 2015 Dec; 5(4): 456–493).

the authors evaluated the effects of (1) neonatal alcohol exposure and (2) an adolescent exercise intervention on the corpus callosum myelination in an animal model of FASD. Diffusion tensor imaging (DTI) scanning is a powerful tool that allows for the non-invasive longitudinal assessment of structural alterations in myelination. Specifically, DTI scanning measures the differences in water movement, or diffusivity, in various biological tissues. The authors proposed two central hypotheses regarding the effect of prenatal alcohol exposure (AE) on white matter tract development: (1) prenatal AE leads to precocial development of corpus callosum in childhood, and (2) prenatal AE leads to a delay in the trajectory of corpus callosum development in adolescence. Obtained findings support the theory that alcohol exposure during pregnancy delays the trajectory of corpus callosum myelination in adolescence. Further, they suggest that voluntary aerobic exercise in adolescence supports forebrain and corpus callosum growth, particularly benefitting the maturation of commissural fibres that are imperative for abstract and perceptual reasoning. Figure 4 shows a DTI image of water diffusivity in tracts in experimental animal.

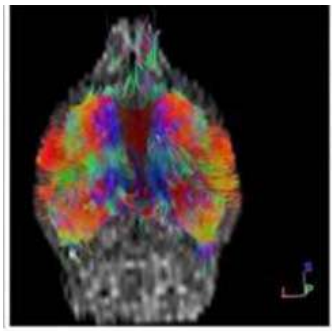

Figure 4. *DTI image of water diffusivity in tracts in experimental rat (Milbocker KA. et al, 2022)*

(Red-blue-green colour schema represents the fibres orientation with red indicating fibres traveling right to left, blue indicating fibres traveling dorsal to ventral, and green indicating fibres traveling in the rostro caudal direction).

Corpus callosum (CC) myelination supports efficient neural signalling between brain hemispheres as well as subcortical to cortical subregions. Myelination of this tract is fundamental to maintain brain growth and circuit refinement during childhood and adolescence. Evidence provided by preclinical and clinical studies indicates that prenatal alcohol exposure (AE) delays the development and myelination of white matter tracts in the adolescent brain. Heavy exposure often results in distinct facial dysmorphologies, delayed growth, and severe cognitive delays in recognizable case of Foetal Alcohol Syndrome. Late-term exposure, however, gives rise to executive function and learning deficits without the hallmark physical dysmorphologies due to their overlap with the brain growth spurt. They are thus more difficult to diagnose. Misdiagnosis with other developmental disorders such as autism spectrum disorder or attention deficit hyperactivity disorder is common. Besides genetic susceptibility, environmental factors in this context - alcohol exposure, and gene-environment interactions are of central interest in research on attention deficit/hyperactivity disorder in children. Focusing on maternal behaviour during pregnancy, prenatal maternal alcohol consumption is associated with behavioural disorders in children [13, 14].

Adaptive behaviour, the ability to respond successfully to everyday demands, may be especially sensitive to the effects of heavy prenatal alcohol exposure. Similar adaptive dysfunction is common in other developmental disorders including attention-deficit/hyperactivity disorder (ADHD). ADHD is frequently present in alcohol-exposed children and this overlap in clinical presentation makes identification of alcohol-exposed children difficult. Direct comparison with children with prenatal alcohol exposure and ADHD may yield distinct patterns of cognitive and behavioural performance and add to the growing knowledge of the neuropsychological and behavioural profiles of prenatal alcohol exposure. Adaptive ability in children with prenatal alcohol exposure is characterized by an arrest in development, as evidenced by a lack of improvement with age in socialization and communication scores. By contrast, children with ADHD exhibit a developmental delay in adaptive ability as their scores continued to improve with age, albeit not to the level of control children. [15].

Prenatal exposure to alcohol often results in disruption to discrete cognitive and behavioural domains, including executive function (EF) and adaptive functioning [16]. In this context, children diagnosed with ADHD manifest similar EC dysfunction like those with a history of prenatal alcohol exposure. Results from various studies suggest that EF deficits are predictive of poorer adaptive behaviour and extend this finding to include children with heavy prenatal exposure to alcohol.

Doyle LR. et al., (2019) [17] tested the relation between general intellectual function and adaptive function in two groups of children: a) with prenatal alcohol exposure and b) control. Although higher intellectual functioning was associated with better adaptive function ability among the controls, this was not found among the alcohol-exposed youth where a general dampening of adaptive ability was noted. The authors hypothesized that, within both IQ ranges, the relationship between IQ and adaptive functioning would be stronger in the nonexposed control group than in the alcohol-exposed group. Moreover, within the alcohol-exposed group, the relationship between adaptive function and IQ would be weaker in the high IQ range than the low IQ range (see fig 5).

Similar results concerning adaptive functioning in foetal alcohol spectrum disorders and the effect of IQ and executive functions are shown by Kautz-Turnbull C. et al. (2021) [18].

Adaptive functioning refers to skills related to everyday life: communication, practical skills, and social skills. Studies show that individuals with FASD have impairments in adaptive functioning much worse than alcohol nonexposed and ADHD groups, regardless of IQ, executive functioning, or age. These results are also confirmed in a previous study by Khoury JE, Milligan K., (2019) [19].

However, attention deficit-hyperactivity disorder (ADHD) is common in foetal alcohol spectrum disorders (FASD) but also in patients without prenatal alcohol exposure (PAE). Many patients diagnosed with idiopathic ADHD may have ADHD and covert PAE, a treatment-relevant distinction [20]. Differential neuroimaging indices in prefrontal white matter in prenatal alcohol-associated ADHD versus idiopathic ADHD. These findings point to tract focal, white-matter pathology possibly specific for ADHD+PAE subjects.

In the investigations of Astley et al. (1995, 2010), using proton magnetic resonance spectroscopy (MRS), the authors demonstrated below-normal levels of choline-compounds (Cho) in children with FASD in white matter of the corona radiata, proximal to the anterior corona radiata (ACR) portion of the tract. O'Neill [20] supposed that low choline level may derive from abnormal choline metabolism; low fractional anisotropy FA suggests suboptimal white-matter integrity in PAE. More advanced MRSI and DTI and neurocognitive assessments may distinguish ADHD+-PAE from ADHD-PAE better, helping therefore to identify covert cases of FASD.

The two aforementioned studies [Kilpatrick LA. et al. in 2021 and Alger JR, et al., 2021] used neuroimaging of supraventricular frontal white matter in children with familial attention-deficit hyperactivity disorder and ADHD due to prenatal alcohol exposure. Two-dimensional magnetic resonance spectroscopic imaging was acquired from supraventricular white matter to measure N-acetyl aspartate compounds, glutamate, creatine + phosphocreatine (creatine), and choline-compounds (choline). Whole brain diffusion tensor imaging was acquired and used to calculate fractional anisotropy, mean, axial, and radial diffusivity from the same super ventricular white matter regions that produced magnetic resonance spectroscopy data. Findings suggest white matter differences between the PAE and familial aetiologies of ADHD. Abnormalities detected by magnetic resonance spectroscopy and diffusion tensor imaging co-localize in supraventricular white matter and are relevant to executive function symptoms of ADHD.

Fan J, et al. (2016) evaluated how white matter deficits mediate the effects of prenatal alcohol exposure on cognitive development in childhood. Heavy exposed children showed lower fractional anisotropy (FA) and higher mean diffusivity (MD) in a subset of regions presented in Fig. 6.

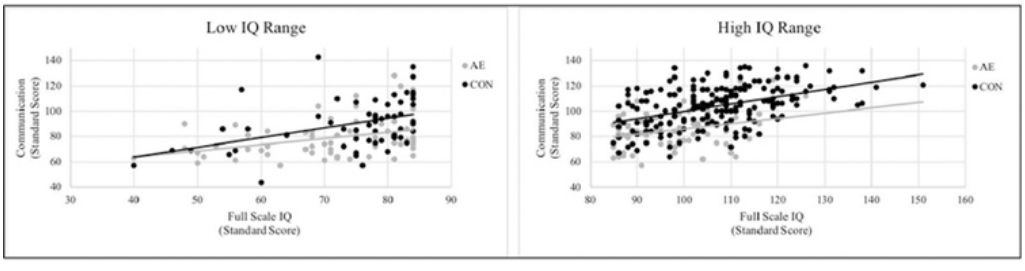

Fig. 5. *Correlation between IQ and adaptive functions (Birth Defects Res. 2019; 111(12): 812–821).*

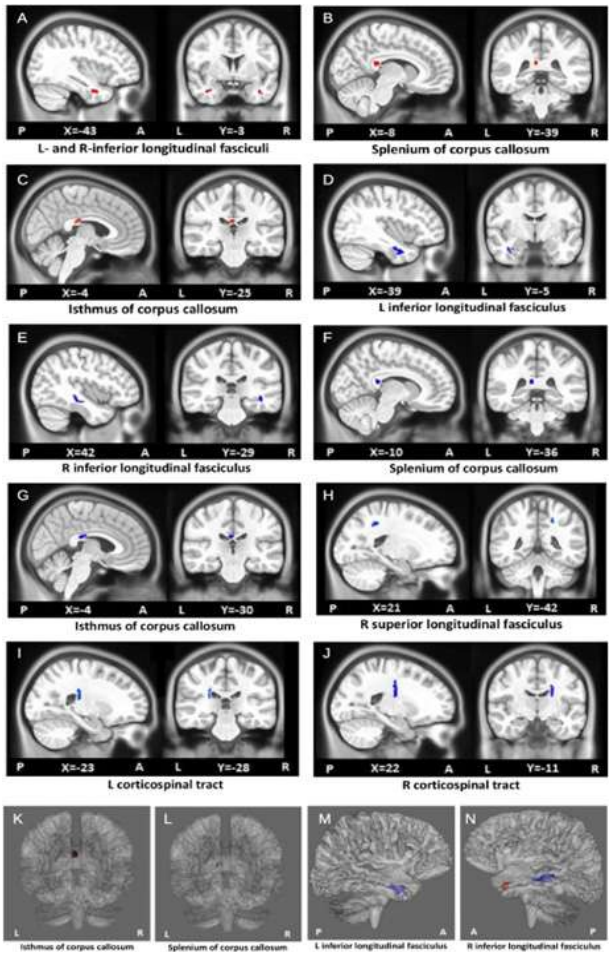

Fig. 6. *Lower fractional anisotropy (FA)and higher mean diffusivity (MD) in a subset of regions as a result of alcohol exposure (Hum Brain Mapp. 2016; 37(8): 2943–2958)*

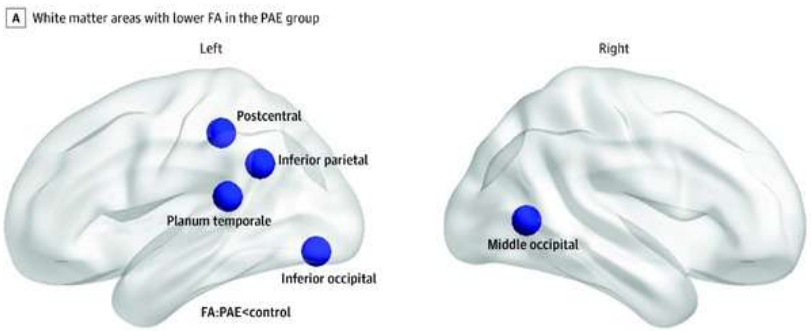

Fig. 7. *Locations of main brain alteration in prenatal alcohol exposure* (JAMA Netw Open. 2022;5(4): e225972).

In a newer study, Long X. et al. (2022) evaluated brain alterations and behaviour in children with low levels of prenatal alcohol exposure (PAE). In this cross-sectional study, children with low levels of PAE had lower fractional anisotropy FA (mean, axial, and radial diffusivity from diffusion tensor imaging) and more behavioural problems compared with a well-matched control group. These results suggest that PAE, even in small amounts, has a measurable effect on brain structure in children (Fig 7).

Roos A et al. (2021) evaluated the influence of alcohol as a pervasive risk factor to neurodevelopment in toddlers. In a selected group of children, aged 30-37 months, they underwent diffusion MRI

on a 3T Siemens scanner during natural sleep and compared the results of children with prenatal exposure with the control group. Children with PAE had altered fractional anisotropy, radial diffusivity and axial diffusivity in brain stem, limbic and association tracts compared to unexposed the control group. Additionally, notably lower fractional anisotropy was found in the uncinate fasciculus, and lower mean and radial diffusivity were found in the fornix stria terminalis and corticospinal tract ($p < 0.05$). There was a significant interaction effect of PAE and prenatal tobacco exposure which lowered the mean, radial and axial diffusivity in the corticospinal tract significantly in the PAE group but not controls. The authors concluded that altered white matter microstructural integrity at 2-3 years of age is consistent with findings in neonates in other cohorts, indicating persistence of effects of PAE through early life. Additionally, prenatal tobacco exposure amplifies effects of alcohol in tracts responsible for motor function. The corticospinal tract is key to motor function extending into the primary motor, premotor and supplementary, and somatosensory cortices. This suggests that it is crucial to consider the effects of alcohol and tobacco together on brain development and, specifically, motor function (see fig 8).

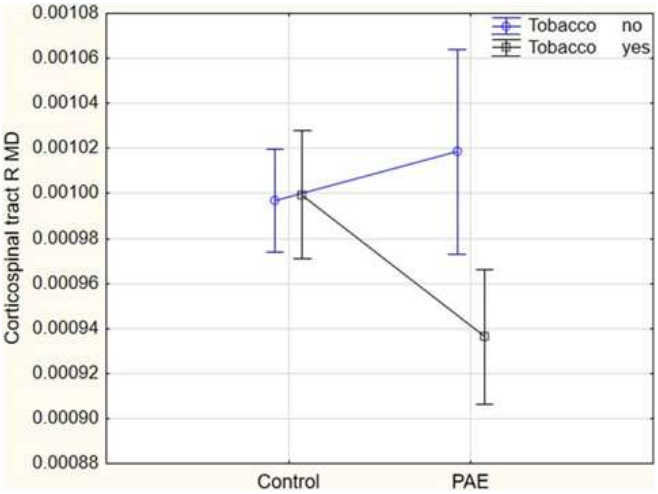

Fig. 8. *Interaction effect of alcohol and tobacco smoking on mean diffusivity in the corticospinal tract. Prenatal tobacco exposure lowered MD in the PAE group but not in controls (Roos A. et al. 2021)*

Similar results are obtained in the study of Kar P, et al. (2021). More precisely, the PAE group had higher FA in the genu of the corpus callosum and lower mean diffusivity in the bilateral uncinate fasciculus. The PAE group also had lower tract volume in the corpus callosum, the bilateral inferior fronto-occipital fasciculi, and the right superior longitudinal fasciculus.

Prenatal alcohol exposure (PAE) has been linked with widespread brain abnormalities including reduced brain volume, altered cortical thickness, and altered white matter connectivity. Additionally, children with PAE are more likely than the general population to experience adverse postnatal exposures such as neglect, poverty, caregiver transitions, abuse (verbal, physical, and sexual), and witnessing violence or chronic substance use. These postnatal experiences can negatively affect brain development [Bick et al., 2015; Hart & Rubia, 2012] and have been associated with increased internalizing (inwardly directed negative behaviours such as anxiety and depression) and externalizing-based problems and disorders (outwardly directed negative behaviours such as aggression and hyperactivity)

PAE has been linked with volume reductions in the frontal lobe [Astley et al., 2009], including the middle frontal gyri in the prefrontal cortex (PFC) [Eckstrand et al., 2012], as well as deep grey matter structures such as the hippocampus and amygdala. White matter also shows widespread effects of PAE, including lower fractional anisotropy (FA), and/or higher mean diffusivity (MD) in limbic tracts, such as the uncinate fasciculus and cingulum.

In the study by Andre QR et al. (2020), the authors hypothesized that children and adolescents with PAE and adverse postnatal exposures would have lower volumes and FA and higher MD in these structures, as well as increased mental health symptoms compared to children with PAE and no postnatal adversity, and unexposed controls. It was predicted there would be cumulative effects of prenatal and postnatal exposures in these regions, such that the combined exposures would result in similar but stronger effects in comparison to those with prenatal alcohol exposure alone.

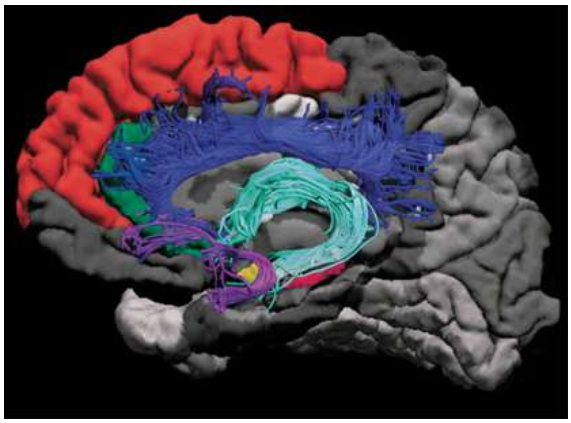

Fig. 10. *Main brain structures altered by alcohol use (Hum Brain Mapp. 2020; 41(15): 4375–4385).*

[For anatomical volumes, the amygdala (yellow), hippocampus (pink), anterior cingulate cortex (green), superior frontal gyrus (red), and the middle frontal gyrus (not shown), were assessed. For DTI tractography, the uncinate fasciculus (magenta), fornix (cyan), and the cingulum (blue), were assessed]

In conclusion, children and youth with PAE had more externalizing symptoms than controls regardless of postnatal exposures, while children with PAE and no postnatal exposures had differences in brain structure from controls. These findings suggest that prenatal exposures and postnatal experiences interact with brain development differently. The unique and divergent effects of adverse exposures, pre- and postnatal, on mental health symptoms and brain developmental trajectories highlights the need for recognition of more PAE research.

Lindlöf A. (2022) analysed the vulnerability of the developing brain, especially the hippocampus related to genetics or toxic influence during development. The study evaluated genes highly expressed throughout the postnatal period in a mouse's hippocampus, especially gene expression from the C57BL/6 mouse hippocampus. These have also been linked to an abnormal phenotype, allowing a greater understanding about hippocampal functions during postnatal development. The results showed that many genes are important for proper embryo development and infant survival, proper growth, and increase in body size, as well as for voluntary movement functions, motor coordination, and balance. The results also indicated an association with seizures that have primarily been characterized by uncontrolled motor activity and the development of proper grooming abilities. The mutational effects mainly refer to lethality prior to or shortly after birth, as most of the genes have been annotated with terms related to preweaning lethality and premature death, and not with other terms related to a later death, such as at or after weaning age (Fig. 10).

As shown before, the corpus callosum is the main connection point between the two brain hemispheres and this structure is especially affected in FAS. Changes are localised in the periventricular zone, where all neurons are born and influence the global development and function of the brain. Alcohol exposure during pregnancy damages the corpus callosum, as it becomes thinner. This can be verified with a foetal MRI. In the first MRI-based study to investigate pre-natal alcohol exposure, researchers found significant changes in the brain structure of foetuses exposed to alcohol compared to healthy controls [36] (Fig 11.)

Most of the previous research confirmed that intrauterine alcohol exposure is associated with a variety of adverse outcomes in offspring. However, few studies have investigated its association with offspring internalizing disorders in late adolescence. Offspring of mothers who consumed alcohol at 18 weeks' gestation were at increased risk of having a diagnosis of depression [Easey KE. et al. 2020].

In spite of the fact that FAS is not a curable condition, new research [Mohammad S. et al., 2020] provides some optimism. It was shown that acute responses to alcohol in progenitor cells altered gene expression in their descendant neurons. Among the altered genes, an increase of the calcium-activated potassium channel Kcnn2 in the motor cortex correlated with motor learning deficits in a mouse model of FASD. The pharmacological blockade of Kcnn2 improves these learning deficits, suggesting Kcnn2 blockers as a new intervention for learning disabilities in FASD. In this context, "Tamapin", an investigational drug derived from Indian red scorpion venom, revers-

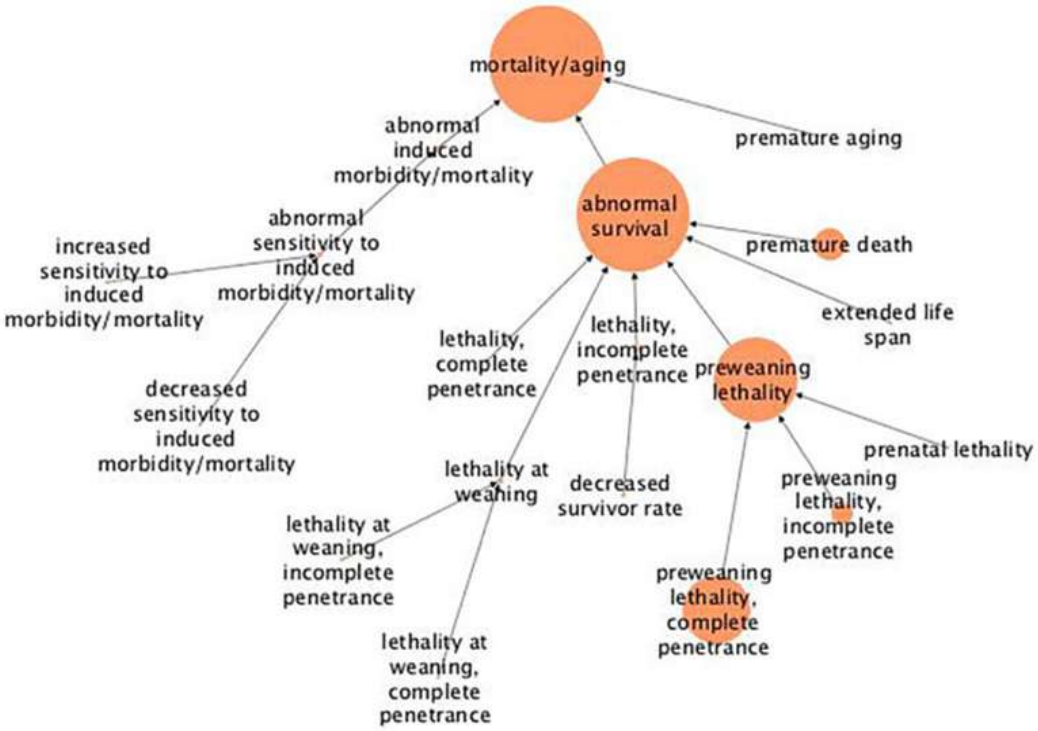

Fig. 10. *Hierarchical tree for the abnormal phenotype mortality/aging* [Lindlöf A. 2022]

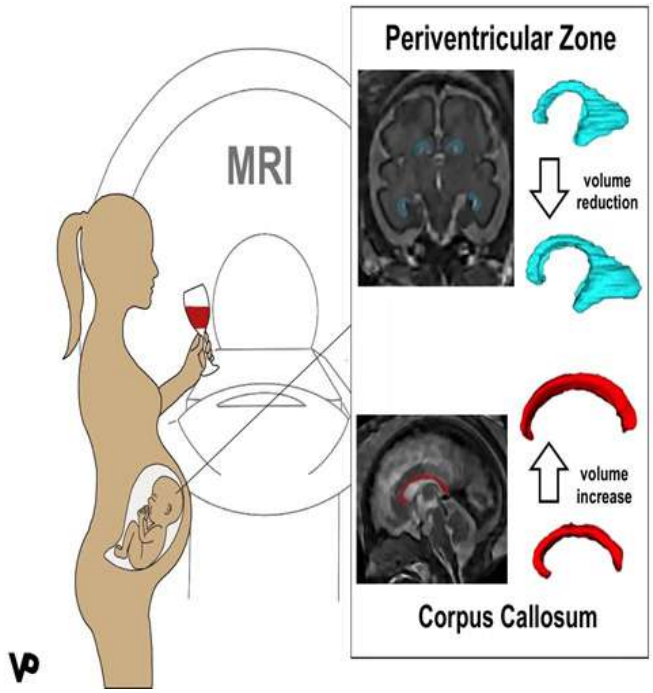

Fig. 11. *Effects of prenatal alcohol exposure (PAE). PAE leads to a volume reduction in the periventricular zone and a volume increase in the corpus callosum*. [Borrowed from RSNA and Marlene Stuempflen, 2021]

es motor deficits in pre-clinical models of foetal alcohol spectrum disorder.

Consequences on the foetus if father consumes alcohol before conception was investigated experimentally in animal models [Conner KE. et al., 2020]. Results showed a significant impact on neocortical development, including abnormal patterns of gene expression within the neocortex and subtle alterations in patterns of intraneocortical connections. These results demonstrate that the developmental impact of preconception alcohol consuming by the father is more harmful than previously thought. This also provides additional insights into the biological mechanisms that may underlie atypical behaviour observed in children of alcoholic fathers.

For mothers who drink alcohol, the negative outcomes of prenatal alcohol exposure on foetal brain development can be reduced with choline supplementation. Increased choline consumption during pregnancy was associated with better performance in tasks requiring sustained attention in children aged seven. Researchers found that doubling the recommended amount of choline by increasing consumption of nuts, eggs, red meats, and fish during pregnancy had the greatest benefits for the developing foetal brain [39, 40].

Ethanol exposure during human third trimester-equivalent period induces persistent impairments in hippocampus-dependent learning and memory [41, 42]. Results from studies suggest neuroimmune activation in response to ethanol within the neonate hippocampus contributes to later-life cognitive dysfunction. Studies suggest that an anti-inflammatory drug may have the potential to stall the damaging effects of alcohol on the foetal brain. The ability of ibuprofen (IBU), a non-steroidal anti-inflammatory drug, to diminish ethanol-induced neuroinflammation and rescue deficits in hippocampus-dependent trace fear conditioning was investigated in experimental rats.

CONCLUSIONS

– The incidence of FASD is not justified but is alarmingly high, provoking significant personal and societal costs.

– The effects of ethanol are expressed on a set of molecules involved in neuroinflammation, myelination, neurotransmission, and neuron function.

– As shown, prenatal exposure of alcohol provokes different phenotypic characteristics together with behavioural changes and cognitive functions.

– Modern neuroimaging techniques allow us to specify some fine structural changes in the affected brain: volume reductions in the frontal lobe, including the middle frontal gyri in the prefrontal cortex, hippocampal structure, interhemispheric connectivity, abnormalities in glial cells, white matter deficits etc.

– Corpus callosum myelination is affected resulting in a lack of the inter-hemispheric connectivity, which is known to facilitate autism, stroke, schizophrenia, as well as dementia, disrupts the cognitive performance, and may lead to neurobehavioral deficits.

– Many symptoms and neuroimaging characteristics are similar in ADHD and FAS.

– It is pointed that the cautious anamnesis for prenatal alcohol and nicotine exposure is very important helping to the real interpretations of clinical symptoms.

– There are some possible ameliorative effects on FAS with ibuprofen, Tamapin, an investigational drug derived from Indian red scorpion venom, or increased choline consumption during pregnancy.

REFERENCES

1. Mewton L, Lees B, Rao RT. Lifetime perspective on alcohol and brain health. BMJ. 2020 Dec 3;371:m4691. doi: 10.1136/bmj.m4691. PMID: 33272963.
2. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (2018)
3. CDC. Fetal alcohol syndrome-Alaska, Arizona, Colorado, and New York, 1995-1997. MMWR Morb Mortal Wkly Rep. 2002; 51(20): 433–5.
4. CDC. Fetal Alcohol Syndrome Among Children Aged 7-9 Years – Arizona, Colorado, and New York, 2010. MMWR Morb Mortal Wkly Rep. 2015; 64(3): 54–57.
5. May PA, Baete A, Russo J, Elliott AJ, Blankenship J, Kalberg WO, Buckley D, Brooks M, Hasken J, Abdul-Rahman O, Adam MP, Robinson LK, Manning M, Hoyme HE. Prevalence and characteristics of fetal alcohol spectrum disorders. Pediatrics. 2014; 134: 855–66.
6. May PA, Gossage JP, Kalberg WO, Robinson LK, Buckley D, Manning M, Hoyme HE. Preva-

lence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. Dev Disabil Res Rev. 2009; 15: 176–92.
7. May PA, Chambers CD, Kalberg WO, Zellner J, Feldman H, Buckley D, Kopald D, Hasken JM, Xu R, Honerkamp-Smith G, Taras H, Manning MA, Robinson LK, Adam MP, Abdul-Rahman O, Vaux K, Jewett T, Elliott AJ, Kable JA, Akshoomoff N, Falk D, Arroyo JA, Hereld D, Riley EP, Charness ME, Coles CD, Warren KR, Jones KL, Hoyme HE. Prevalence of Fetal Alcohol Spectrum Disorders in 4 US Communities. Journal of American Medical Association. 2018; 319(5): 474–482
8. Krulewitch CJ. Alcohol consumption during pregnancy. Annual Review of Nursing Research. 2005; 23: 101–134.
9. Gao, L. et al. Granger causal time-dependent source connectivity in the somatosensory network. Sci. Rep. 2015; 5, 10399;
10. Hashimoto JG, Wiren KM, Wilhelm CJ. A neurotoxic alcohol exposure paradigm does not induce hepatic encephalopathy. Neurotoxicol Teratol. 2016 Jul-Aug; 56: 35–40.
11. Basavarajappa BS. Fetal Alcohol Spectrum Disorder: Potential Role of Endocannabinoids Signaling. Brain Sciences. 2015; 5(4): 456–493.
12. Savage LM, Nunes PT, Gursky ZH, Milbocker KA, Klintsova AY. Midline Thalamic Damage Associated with Alcohol-Use Disorders: Disruption of Distinct Thalamocortical Pathways and Function. Neuropsychology Review. 2021 Sep; 31(3): 447–471
13. Burger PH, Goecke TW, Fasching PA, Moll G, Heinrich H, Beckmann MW, Kornhuber J. Einfluss des mütterlichen Alkoholkonsums während der Schwangerschaft auf die Entwicklung von ADHS beim Kind [How does maternal alcohol consumption during pregnancy affect the development of attention deficit/hyperactivity syndrome in the child]. Fortschr Neurol Psychiatr. 2011 Sep; 79(9): 500–6.
14. Walloch JE, Burger PH, Kornhuber J. Was wird aus Kindern mit fetalem Alkoholsyndrom (FAS)/fetalen Alkoholspektrumstörungen (FASD) im Erwachsenenalter? [What is known about the outcome as adults for children with fetal alcohol syndrome (FAS)/fetal alcohol spectrum disorders (FASD)?]. Fortschr Neurol Psychiatr. 2012 Jun; 80(6): 320–6.
15. Crocker N, Vaurio L, Riley EP, Mattson SN. Comparison of adaptive behavior in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. Alcohol Clin Exp Res. 2009 Nov; 33(11): 2015–23.
16. Ware AL, Crocker N, O'Brien JW, Deweese BN, Roesch SC, Coles CD, Kable JA, May PA, Kalberg WO, Sowell ER, Jones KL, Riley EP, Mattson SN; CIFASD. Executive function predicts adaptive behavior in children with histories of heavy prenatal alcohol exposure and attention-deficit/hyperactivity disorder. Alcohol Clin Exp Res. 2012 Aug; 36(8): 1431–41.
17. Doyle LR, Coles CD, Kable JA, May PA, Sowell ER, Jones KL, Riley EP, Mattson SN; CIFASD. Relation between adaptive function and IQ among youth with histories of heavy prenatal alcohol exposure. Birth Defects Res. 2019 Jul 15; 111(12): 812–821.
18. Kautz-Turnbull C, Petrenko CLM. A meta-analytic review of adaptive functioning in fetal alcohol spectrum disorders, and the effect of IQ, executive functioning, and age. Alcohol Clin Exp Res. 2021 Dec; 45(12): 2430–2447.
19. Khoury JE, Milligan K. Comparing Executive Functioning in Children and Adolescents With Fetal Alcohol Spectrum Disorders and ADHD: A Meta-Analysis. J Atten Disord. 2019 Dec; 23(14): 1801–1815.
20. O'Neill J, O'Connor MJ, Yee V, Ly R, Narr K, Alger JR, Levitt JG. Differential neuroimaging indices in prefrontal white matter in prenatal alcohol-associated ADHD versus idiopathic ADHD. Birth Defects Res. 2019 Jul 15; 111(12): 797–811.
21. Astley SJ, Weinberger E, Shaw D, Richards T, Clarren SK (1995). Magnetic resonance imaging and spectroscopy in fetal ethanol exposed Macaca nemestrina. Neurotoxicology and Teratology, 17, 523–530.
22. Astley, S. (2010). Profile of the first 1,400 patients receiving diagnostic evaluation for fetal alcohol Spectrum disorders at the Washington state fetal alcohol syndrome diagnostic & prevention network. Canadian Society of Pharmacology and Therapeutics, 17(1), 132–164.
23. Kilpatrick LA, Joshi SH, O'Neill J, Kalender G, Dillon A, Best KM, Narr KL, Alger JR, Levitt JG, O'Connor MJ. Cortical gyrification in children with attention deficit-hyperactivity disorder and prenatal alcohol exposure. Drug Alcohol Depend. 2021 Aug 1;225: 108817.
24. Alger JR, O'Neill J, O'Connor MJ, Kalender G, Ly R, Ng A, Dillon A, Narr KL, Loo SK, Levitt JG. Neuroimaging of Supraventricular Frontal White Matter in Children with Familial Attention-Deficit Hyperactivity Disorder and Attention-Deficit Hyperactivity Disorder Due to Prenatal Alcohol Exposure. Neurotox Res. 2021 Aug;39(4):1054-1075. doi: 10.1007/s12640-021-00342-0. Epub 2021 Mar 22.
25. Fan J, Lin R, Xia S, Chen D, Elf SE, Liu S, Pan Y, Xu H, Qian Z, Wang M, Shan C, Zhou L, Lei QY, Li Y, Mao H, Lee BH, Sudderth J, DeBerardinis RJ, Zhang G, Owonikoko T, Gaddh M,

Arellano ML, Khoury HJ, Khuri FR, Kang S, Doetsch PW, Lonial S, Boggon TJ, Curran WJ, Chen J. Tetrameric Acetyl-CoA Acetyltransferase 1 Is Important for Tumor Growth. Mol Cell. 2016 Dec 1; 64(5): 859–874. doi: 10.1016/j.molcel.2016.10.014. Epub 2016 Nov 17.

26. Long X, Lebel C. Evaluation of Brain Alterations and Behavior in Children With Low Levels of Prenatal Alcohol Exposure. JAMA Netw Open. 2022 Apr 1; 5(4): e225972.
27. Roos, A., Wedderburn, C. J., Fouche, J.-P., Subramoney, S., Joshi, S. H., Woods, R. P., Zar, H. J., Narr, K. L., Stein, D. J., & Donald, K. A. (2021). Central white matter integrity alterations in 2-3-year-old children following prenatal alcohol exposure. Drug and Alcohol Dependence, 225, 108826.
28. Kar, P., Reynolds, J. E., Grohs, M. N., Gibbard, W. B., McMorris, C., Tortorelli, C., & Lebel, C. (2021). White matter alterations in young children with prenatal alcohol exposure. Developmental Neurobiology, 81, 400– 410.
29. Bick, J., & Nelson, C. A. (2016). Early adverse experiences and the develop-ing brain.Neuropsychopharmacology,41(1), 177–196.
30. Hart, H., & Rubia, K. (2012). Neuroimaging of child abuse: A critical review.Frontiers in Human Neuroscience,6(March), 1–24.
31. Astley, S., Aylward, E. H., Carmichael Olson, H., Kerns, K., Brooks, A.,Coggins, T. E.,... Richards, T. (2009). Magnetic resonance imaging out-comes from a comprehensive magnetic resonance study of childrenwith fetal alcohol spectrum disorders.Alcoholism: Clinical and Experi-mental Research, 33(10), 1671–1689.
32. Eckstrand, K. L., Ding, Z., Dodge, N. C., Cowan, R. L., Jacobson, J. L.,Jacobson, S. W., & Avison, M. J. (2012). Persistent dose-dependentchanges in brain structure in young adults with low-to-moderate alco-hol exposure in utero.Alcoholism: Clinical and Experimental Research,36(11), 1892–1902.
33. Andre QR, McMorris CA, Kar P, Ritter C, Gibbard WB, Tortorelli C, Lebel C. Different brain profiles in children with prenatal alcohol exposure with or without early adverse exposures. Hum Brain Mapp. 2020 Oct 15; 41(15): 4375–4385.
34. Lindlöf A. The Vulnerability of the Developing Brain: Analysis of Highly Expressed Genes in Infant C57BL/6 Mouse Hippocampus in Relation to Phenotypic Annotation Derived From Mutational Studies. Bioinform Biol Insights. 2022 Jan 5; 16:11779322211062722.
35. Kasprian G, Schwartz E, Diogo M, Glatter S, Pfeiler B, Schmidbauer V, Bartha-Doering L, Seidl R, Krampl-Bettelheim E, Prayer D. (2021) MRI Reveals Altered Brain Structure in Fetuses Exposed to Alcohol, Neuroscience, 2021 RSNA
36. Easey KE, Timpson NJ, Munafò MR. Association of Prenatal Alcohol Exposure and Offspring Depression: A Negative Control Analysis of Maternal and Partner Consumption. Alcoholism, Clinical and Experimental Research. 2020 May; 44(5): 1132–1140.
37. Mohammad S, Page SJ, Wang L, Ishii S, Li P, Sasaki T, Basha A, Salzberg A, Quezado Z, Imamura F, Nishi H, Isaka K, Corbin JG, Liu JS, Kawasawa YI, Torii M, Hashimoto-Torii K. Kcnn2 blockade reverses learning deficits in a mouse model of fetal alcohol spectrum disorders. Nat Neurosci. 2020 Apr;23(4):533-543.
38. Conner KE, Bottom RT, Huffman KJ. The Impact of Paternal Alcohol Consumption on Offspring Brain and Behavioral Development. Alcohol Clin Exp Res. 2020 Jan;44(1):125-140.
39. Irina N. Zakharova, Irina V. Berezhnaya, Aleksandra I. Sgibneva, Choline deficiency in the body, clinical manifestations and long-term consequences, Pediatrics. Consilium Medicum, 10 .26442/26586630.2022.1.201510, 1, (66–71), (2022).
40. Bahnfleth, C.L., et al. (2022) Prenatal choline supplementation improves child sustained attention: A 7-year follow-up of a randomized controlled feeding trial. The FASEB Journal. doi. org/10.1096/fj.202101217R.
41. Goodfellow MJ, Shin YJ, Lindquist DH. Mitigation of postnatal ethanol-induced neuroinflammation ameliorates trace fear memory deficits in juvenile rats. Behav Brain Res. 2018 Feb 15; 338: 28–31.
42. Chen, YN., Sha, HH., Wang, YW. et al. Histamine 2/3 receptor agonists alleviate perioperative neurocognitive disorders by inhibiting microglia activation through the PI3K/AKT/FoxO1 pathway in aged rats. J Neuroinflammation 17, 217 (2020). https://doi.org/10.1186/s12974-020-01886-2.

Резиме

КАКО АЛКОХОЛОТ ГО ОШТЕТУВА РАЗВОЈОТ НА МОЗОКОТ КАЈ ДЕЦАТА

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И покрај сознанието дека алкохолот има тешки здравствени последици, насекаде низ светот луѓето пијат за да се социјализираат, да прославуваат или да се релаксираат. Три периоди во динамичните мозочни промени се особено чувствителни за штетните последици од алкохолот: гестацијата (од зачнување до раѓање), доцната адолесценција (15–19 години) и постарата возрасна група (над 65 години). Овој напис е насочен само на негативните последици на алкохолот кај деца што биле изложени на оваа хемикалија пред раѓањето, ентитет познат како фетален алкохолен синдром (ФАС).

Овој ревијален труд е базиран на публикувани статии во ПубМед објавени во последните две децении и содржи анализа на над 150 трудови.

Употребата на алкохол за време на бременоста може да предизвика спонтани абортуси, мртвородени и цела палета долгорочни физички, бихевиорални и интелектуални попреченост. Ефектите на етанолот се изразени врз група молекули што се вклучени во невроинфламацијата, миелинизацијата, невротрансмисијата и невралната функција.

Модерните невроимиџинг-техники овозможија спецификација на фини структурни промени во оштетениот мозок: редукција на волуменот на фронталниот лобус, вклучително на средниот фронтален гирус во префронталната кора, промени во хипокампусната структура, интерхемисферискa поврзаност, абнормалности во глија-клетките, дефицит во белата маса итн. Како резултат од дефицитарната интерхемисферична поврзаност, засегната е миелинизацијата на корпус калозум, состојба што може да предизвика аутизам, мозочен удар, шизофренија, деменција, како и растројство на когнитивните вештини и невробихевиорални дефицитарности.

Нагласено е дека многу симптоми и невроимиџинг карактеристики се слични кај АДХД и ФАС, така што е неопходна прецизна анамнеза за пренатална експозиција на алкохол и никотин за да се направи реална интерпретација на клиничките симптоми..

Клучни зборови: фетален алкохолен синдром, невропсихолошки карактеристики, невроимиџинг, модерен приод