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# HIPPOCAMPAL ALTERATIONS AND COGNITIVE IMPAIRMENT IN SWISS ALBINO MICE EXPOSED TO PRENATAL ZIDOVUDINE

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## ABSTRACT

**Introduction:** Exposure to drugs in utero may induce developmental alterations, including impaired growth, birth defects, and altered brain development. Zidovudine (ZDV) with a chemical name AZT, is a thymidine analog, exhibits teratogenic and neurotoxic effects. Nevertheless, it remains an essential nucleoside reverse transcriptase inhibitor utilized in HAART for HIV-infected mothers to prevent maternal-to-child transmission of HIV. **Objective:** This study aimed to identify prenatal zidovudine-induced histopathological changes in the hippocampus and the associated cognitive alterations in Swiss albino mice. **Methods:** Pregnant Swiss albino mice were divided into two groups: Control and Treated, with six mice per group. The treated group was orally administered ZDV at a dose of 50 mg/kg bwt from gestation day 6$^{th}$ to 15$^{th}$. Three pregnant mice from each group were allowed to deliver and pups at 8 weeks were subjected to Morris Water Maze test to analyze the cognitive changes. The remaining three pregnant mice from both the control and treated groups were sacrificed on the 18th day of gestation and fetuses were subjected for hippocampal histopathology using H&E staining. **Results:** The Morris water maze test revealed impairment of spatial learning and memory in the prenatal treated group. Microscopic examination of the hippocampus revealed degeneration and reduction of the migrating neuroblast cells. A substantial reduction in the density of neuroblast cells by enhanced apoptosis leads to empty spaces giving a spongy appearence in the hippocampus. **Conclusion:** The findings of this research demonstrate that prenatal ZDV exposure induces profound alterations in hippocampal structure, resulting in spatial learning and memory defects. Consequently, ZDV administration during pregnancy should be approached with caution.

**Keywords:** Cognition test, Morris water maze test, Zidovudine, *Azidothymidine,* HIV drug, HAART, hippocampal histology.

## INTRODUCTION

Zidovudine (ZDV), which is known with a chemical name azidothymidine (AZT) (1), is a thymidine analog, and recognized as one of the medications exhibiting strong in vitro efficacy against Human Immunodeficiency Virus (HIV) replication in human T4 lymphocyte cell lines (2). It serves as the foundation for antiretroviral therapy (ART) during pregnancy in humans (3). The active form of zidovudine, known as zidovudine triphosphate, effectively inhibits

HIV replication. Zidovudine when administered in a three-stage protocol after conception, during delivery, and for six weeks following birth can decrease the likelihood of HIV transmission from mother to child by 8% (2).

When administered orally, zidovudine is swiftly and fully absorbed by the mother's digestive system, reaching its highest concentration in the bloodstream within approximately 30 minutes. The bioavailability of the drug is 60%, with the remaining 40% undergoing initial metabolic processing in the liver. ZDV is eliminated from the body through glucuronidation (50-60%) and kidney excretion (10-20%). This medication can penetrate both the placental barrier and the blood-brain barrier, achieving a concentration in the cerebrospinal fluid of that–15-35% of its plasma levels(3).

Birth defects in humans are linked to zidovudine exposure, including abnormalities of the diaphragm, heart, central nervous system, and skeletal system, cleft palate, extra fingers or toes, blue sclera, and stunted growth(4). Additionally, infants exposed to ZDV before birth experience reduced insulin levels, leading to fetal diabetes(5).

Hippocampus is crucial for learning and memory as well as the regulation of sexual and emotional behaviors (6). In mature brains, certain areas of the hippocampus maintain high plasticity and can regenerate cells that have reached the end of their functional learning (7).

While the teratogenic effects of ZDV have been established, there is a lack of research on how ZDV impacts cognitive function in first-generation offspring and the associated hippocampal microanatomy. Our experimental design aimed to investigate the ZDV-induced changes in the fetal hippocampus and their influence on spatial learning and memory in Swiss albino mice exposed to the drug prenatally.

## MATERIALS AND METHODS

Ethical approval was obtained from the Central Animal Ethical Committee of the Institute of Medical Sciences BHU before the start of the study. The CPCSEA guidelines were strictly followed while providing housing and handling of mice. The study was carried out in the animal house of the Department of Anatomy, on 2 months aged Swiss Albino female mice weighing 20-25 g.

These mice were kept for mating, and later, pregnant Swiss albino mice were separated from the cage and divided into two groups.

The experimental group received ZDV orally at a dose of 50 mg/kg from gestation days 6-15. Distilled water was administered to the control group following the same schedule. Both groups, each comprising of three pregnant Swiss albino mice, were further subdivided. The offspring of one subgroup were raised till 8 weeks and then allowed to undergo cognitive assessment using Morris Water Maze (MWM) test. The other subgroup was euthanized on day 18 of gestation via cervical dislocation. The fetuses were extracted via laparotomy and preserved in 10% formalin, and the brains were removed for microscopic analysis. Hippocampal sections were prepared and stained with hematoxylin and eosin for histopathological examination(Mishra et al., 2018).

Morris Water Maze Test

The Morris water maze test was performed to assess the learning and spatial memory of mice. The test was performed in three sessions: acquisition, probe trial, and reverse acquisition.

The experiment used a circular black pool (1.4 m in diameter, 80 cm high) filled with water at 25°C to a depth of 44 cm. The pool is divided into four quadrants by marking them on the wall. Initially, all pups were introduced to the water maze for 1 minute and taught to climb onto a visible circular platform. The following day, a place acquisition test was conducted with the platform submerged 1 cm below the water surface in the center of one quadrant. This platform location remained constant throughout the 5-day training period. Each session began with the generation of five random sequences of four starting points along the perimeter of the pool. All the mice followed this sequence for each session. In subsequent sessions, each mouse was placed in the water facing the wall at the designated starting point and given 90 seconds to locate the hidden platform. Upon reaching the platform (escape latency), the animals were allowed a 20-second rest period. The time taken to locate the platform was recorded.

To evaluate the memory of the mice, researchers conducted a probe trial test, which measured the duration the animals spent in the quadrant where the platform was originally located but was subsequently removed. Additionally, a reverse acquisition test was used to examine spatial learning abilities. In this test, the hidden platform was relocated from its initial position to the opposite quadrant during the acquisition trial.

## RESULTS

The present study was based on the observation of alterations in the learning and memory of mice prenatally exposed to ZDV. A standardized behavioral test, ie, Morri's water maze test, was used to study changes in the learning and memory of mice pups once they reached 8 weeks of age. A microscopic study of the hippocampus was conducted in fetal mice to visualize the histopathological changes caused by ZDV, which led to impaired learning and memory in the treated group.

Morris water maze test:

In the acquisition session (Table 01[1]), the time taken to find the hidden platform (escape latency) increased in the treated group, which was statistically significant as compared with that in the control group ($p<0.05$).

The control mice spent more time looking for the removed platform in designated quadrant in the probe trial test (Table 02[2]), than the treated mice and this difference was statistically significant ($p<0.05$). This indicates a loss of spatial memory in the treated mice.

In the reverse acquisition trial (Table 03[3]), control mice took less time to find the hidden platform in the opposite quadrant than the treated mice which was statistically significant ($p<0.05$). This indicates a deficient learning capacity in the treated mice.

The results of all these trials of Morris water maze test indicate significant decrease in spatial learning and memory of prenatal zidovudine treated mice.

Histological findings:

Zidovudine induces degeneration of neuroblasts in the hippocampus (Fig.1). The neuroblast show clumping of cells with pyknotic nucleus ultimately leading to degeneration of cells (Fig.2). This results in reduced density of cells with enhanced glial reaction leading to spongiform appearance and gliosis in hippocampus (Fig.3).

**DISCUSSION**

Zidovudine, a key component of antiretroviral therapy (ART), functions as a reverse transcriptase inhibitor and is used in combination drug treatments to prevent mother-to-child HIV transmission. The brain and cognitive development of children can be impacted by ART through both direct and indirect means. Direct effects occur when children themselve are administered ART, whereas indirect effects result from prenatal exposure to ART (9).

Zidovudine is rapidly absorbed in the intestine and can cross placenta & blood brain barrier in significant amount. In this research, mice dam was administered 50 mg/kg of the drug individually, as this produces a therapeutic plasma level like that in humans (10). Research has shown that even a single 150 mg/kg dose of ZDV, combined with trace amounts of 14C-ZDV, administered to pregnant rats resulted in higher ZDV concentrations in the fetal brain than in the spinal cord (11). Zuena et al. found that offspring exposed to zidovudine in the womb had considerable zidovudine concentrations in their brains.

Zidovudine is also known as azidothymidine (AZT), but researchers claim that a lot of modifications has been carried out in its structure to increase the activity and reduce toxicity. AZT is said to have poor ability to cross the blood-brain barrier (BBB) to reach CNS. Even though, the effects of prolonged use of AZT are same as that of zidovudine which are mania, psychosis, myopathy, and other central nervous system diseases (1).

Research indicates that ZDV causes mitochondrial dysfunction and related neuropathies, that negatively affect spatial learning and memory (2). The results of the acquisition and probe trial tests in this study ($p<0.05$) demonstrated impaired spatial learning and memory in mice treated with zidovudine, potentially due to mitochondrial dysfunction and associated neuropathies. Reduced creatine kinase (CK) levels affect the brain's energy status, leading to behavioral alterations. ZDV reduces CK levels by causing mitochondrial and l-carnitine depletion, resulting in increased apoptosis of brain cells. It also elevates Reactive Oxygen Species (ROS) production, causing oxidative damage to the brain (12). Furthermore, adult mice exposed to ZDV exhibit decreased expression of hippocampal metabotropic and ionotropic glutamate receptors (2)**.**

Brain-derived neurotrophic factor (BDNF) is crucial for neuronal survival and development. It functions as a neurotransmitter modulator and contributes to neuronal plasticity, which is vital for cognitive processes, such as learning and memory formation. Studies have shown elevated BDNF concentrations in several brain regions, including the parietal cortex, hippocampus, and hypothalamus, of adult mice exposed to zidovudine. Excessive BDNF in the hippocampus may impair normal learning and memory due to heightened excitability in learning circuits or excessive plasticity, resulting in synaptic refinement (13). Notably, the increase in BDNF levels within the hippocampal region differed between male and female zidovudine-treated mice. Additionally, zidovudine administration leads to higher Nerve Growth Factor (NGF) levels in the hippocampus of female mice, potentially enhancing neuronal plasticity and disrupting learning processes (14).

Various regions of the brain have been examined using multiple methods, including electrophysiological recordings, light microscopic measurements, and diverse molecular biological and histochemical techniques, to investigate neurological disorders, pathophysiological alterations, and potential drug treatments (15). ZDV causes histopathological changes in the fetal brain, such as microcystic degeneration of the cerebral cortex (16). In our study, H&E-stained hippocampal sections from ZDV-treated subjects exhibited signs of neurodegeneration and disruption of the normal laminar structure. The migration of neuroblasts was impaired owing to degeneration and clumping, and pyknotic cells surrounded by empty vacuolar spaces were observed. These histological alterations in the hippocampus

[1] Table 01: Acquisition trial of Morris water maze test for different group of mice.

[2] Table 02: Probe trial of Morris water maze test for different group of mice.

[3] Table 03: Reverse acquisition trial of Morris water maze test for different group of mice.

likely account for the modified results of the Morris water maze test (MWM), suggesting compromised learning and memory functions.

Research by Yang et al. employed ZDV to disrupt neurogenesis during rat organogenesis. Their MWM test results corroborated our findings, revealing increased escape latency ($p < 0.01$) and time in the target quadrant ($p < 0.01$) for ZDV treated rats. Additionally, probe trial results suggested that ZDV administration impairs spatial cognition (17,18). A separate study by Tsai et al. found that rats given ZDV exhibited markedly poorer performance in both acquisition and probe tests compared to the control group and those treated with alternative drugs (19).

In addition to interfering with neurogenesis, ZDV amplifies the release of corticosterone when exposed to acute stress, elevates oxidative stress in the brain, and diminishes the expression of glutamate receptors in the hippocampus. Furthermore, it inhibits the memory-preserving effect, resulting in a deficit in long-term memory (17).

Previously, high doses of ZDV monotherapy have been linked to various psychological effects, including hallucinations, psychosis, mania, and depression (18). This phenomenon may be attributed to role of combined ART (CART) in enhancing β-amyloid protein (Aβ) production by inhibiting microglial phagocytosis, which normally clears Aβ. This leads to increased Aβ aggregation and deposition, resulting in neurotoxicity (19).

Research has demonstrated that exposure to zidovudine in the initial half of mouse gestation not only reduces the number of fetuses per mouse, but also decreases the crown-rump length of surviving fetuses due to inhibited cell division (20). Similarly, zidovudine exhibits bactericidal properties against Enterobacteriaceae, demonstrating the ability to eradicate E. coli in a 3-hour timeframe. This property stem from its function as a DNA chain terminator (21).

In conclusion, our current findings, along with previous research, indicate that ZDV can penetrate the placental barrier and reach the fetal brain, thus indirectly affecting normal brain development. Although the connection between neurogenesis and memory remains uncertain, the neurotoxic effects of ZDV on the developing hippocampus of fetuses result in diminished learning and memory capabilities in mouse offspring.

## CONCLUSION

Before administering zidovudine as a part of HAART (highly active antiretroviral therapy), it is crucial to consider its potential teratogenic impact on the fetus. Although not classified as a class-D drug like lamivudine or efavirenz, zidovudine still poses significant risks to brain development. The findings of this study demonstrate the harmful effects of ZDV on cognitive function and behavior, including microscopic tissue alterations in hippocampus, indicating the need for cautious use during pregnancy. Additionally, children exposed to ZDV in utero may require ongoing monitoring and cognitive evaluation. Further investigation is necessary to develop methods to reduce these adverse outcomes.

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**Tables**:

**Table 01: Acquisition trial of Morris water maze test for different group of mice**

| S.No. | N | Mean | Std. Deviation (+/-) | 95% Confidence Interval for Mean | | Significance |
|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | |
| 1 | 5 | 33.6 | 2.60768 | 30.3621 | 36.8379 | |
| 2 | 5 | 41.6 | 2.60768 | 38.3621 | 44.8379 | 0.012* |

**Table 02: Probe trial of Morris water maze test for different group of mice**

| S.No | N | Mean | Std. Deviation (+/-) | 95% Confidence Interval for Mean | | Significance |
|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | |
| 1 | 5 | 45.4 | 2.40832 | 42.4097 | 48.3903 | |
| 2 | 5 | 30 | 5.47723 | 23.1991 | 36.8009 | 0.011*[4] |

[4] *shows statistical significance of p value, ie., p>0.05.

**Table 03: Reverse acquisition trial of Morris water maze test for different group of mice**

| S.No. | N | Mean | Std. Deviation (+/-) | 95% Confidence Interval for Mean | | Significance |
|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | |
| 1 | 5 | 34.4 | 1.67332 | 32.3223 | 36.4777 | |
| 2 | 5 | 44 | 3.16228 | 40.0735 | 47.9265 | 0.023* |

Figures:

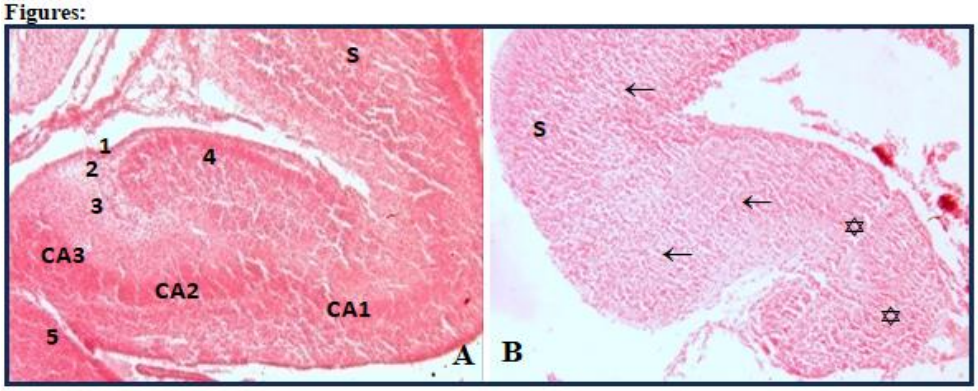


**Fig. 1: H &E stained hippocampus of fetal mice x 100X.**

A. Control group: Showing 5 layers. 1. ventricular zone, 2. subventricular zone, 3. intermediate zone, 4. dentate gyrus (DG) and 5. fimbria. Subiculum (S), CA1, CA2, CA3 regions are differentiable. B. Treated group: Showing degeneration of neuroblast (←). Loss of laminar pattern (✡).

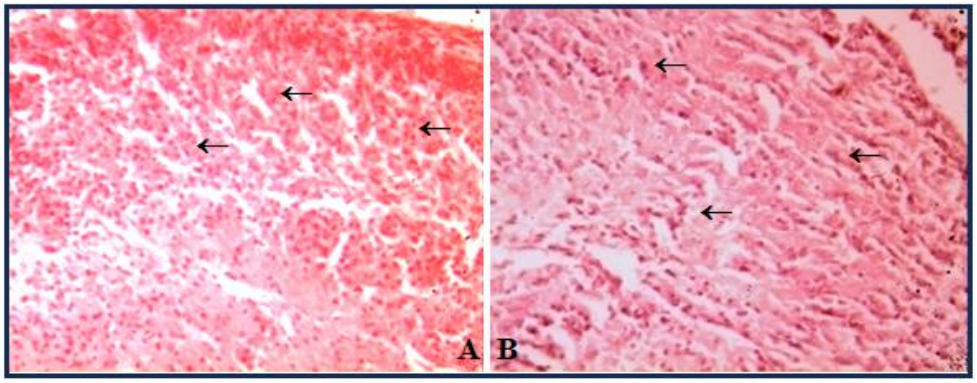


**Fig. 2: H & E stained hippocampus of fetal mice x 400X.**

A. Control - Showing migrating neuroblast (←). B. Treated group: Showing reduced migration and degeneration of neuroblast (←)

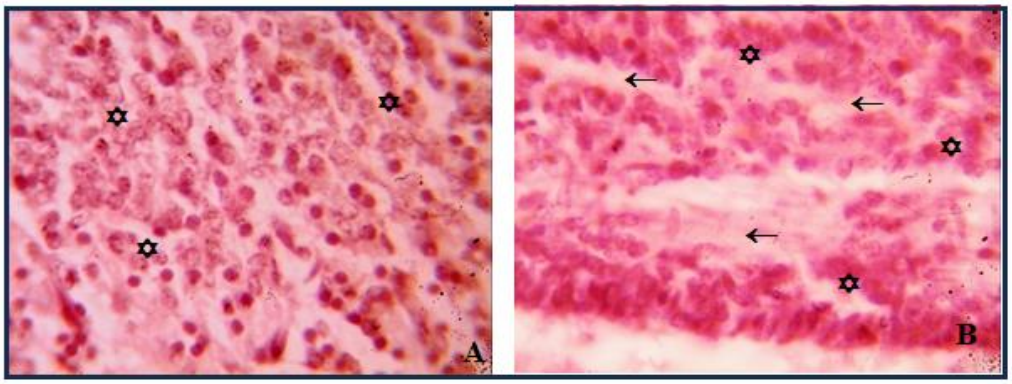


**Fig. 3: H & E stained hippocampus of fetal mice x 1000X.**

A. Control - Showing migrating neuroblast (nucleus surrounding ✡). B. Treated group: Showing degenerated and clumped neuroblast (✡). Showing pyknotic cell with empty vacuolar spaces (←).

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