ORIGINAL RESEARCH PAPER

Anatomy

PRENATAL ZIDOVUDINE INDUCED TOXIC CHANGES IN CEREBRUM OF SWISS ALBINO MICE

KEY WORDS: LGBT, CIM, NBA, TSC

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ABSTRACT

Aims & objective : zidovudine a nucleoside reverse transcriptase inhibitor is used in HIV infected mothers to prevent maternal to child transmission of HIV. However its effect on the cerebrum of developing embryo has not ben explored till yet.
Material & methods: zidovudine was given to pregnant mice in the dose of 50mg/kgbw, 100mg/kgbw & 150mg/kgbw and the cerebrum of 18th day fetus was studied for any gross or microscopic anomaly.
Results : zidovudine induced a dose dependent degeneration and deficient migration of neuroblasts leading to empty vacuolar spaces & loss of cytoarchitecture in cerebral cortex of developing mice.
Conclusion : zidovudine is deleterious to cerebral cortex of embryo so should be used cautiously by physicians.

Introduction

The acquired immune deficiency syndrome (AIDS) is a potentially fatal transmissible disease caused by Human Immuno Deficiency Virus type-1 (HIV-1). Widely recognized as the most significant new infectious disease to emerge during the twentieth century.

Since the discovery of the acquired immuno deficiency syndrome (AIDS) in 1981, considerable progress has been made in the development of agents with anti-HIV activity. There are several drugs available, interfering with different steps in HIV's replication cycle.

Zidovudine was one of the first 2'-3'-dideoxynucleosides to cause inhibition of human immunodeficiency virus (HIV) replication in vitro. It was the first antiretroviral agent to demonstarte clinical efficacy in patients infected with HIV and was introduced in 1987 for the treatment of AIDS[1]

Zidovudine belongs to a class of antiretroviral drug called as Nucleoside Reverse Transcriptase Inhibitors (NRTIs). Zidovudine is a prodrug and must be phosphorylated in lymphocytes in order to exert its antiviral action[2].

Although used widely the effect of zidovudine on brain of developing fetus is still less explored.

Material and method

Prior approval of institutional ethical committee was taken before the start of the present study. For this study swiss albino female mice were taken and were kept with male mice for mating overnight in the ratio of 3:1. Presence of vaginal plug was considered to be the first day of gestation (GD 0). The pregnant female mice were divided into four groups for the present study. The first group was designated as control and was given tap water by gavage from day6 to 16 of gestation. The other three groups were designated as treated and were given zidovudine in the dose of 50mg/kg, 100mg/kg and 150mg/kg respectively by gavage for the same period. On day 18th of gestation the female mice was sacrificed by cervical dislocation and uterotomy was done to extract the embryos. The brain of the embryos were dissected out and kept in formalin for fixation. For histological study the brain was processed, sections were cut and stained with hematoxylin and eosin.

Observation

There was no significant reduction in weight of cerebrum of treated mice as compared to the control nor there was any overt structural anomaly in the cerebrum of treated mice. On histological examination of cerebral cortex of control mice we can see the migrating neuroblasts from ventricular zone to cortical plate (figure 1 & 2). However on microscopic examination the following changes in the cerebral cortex of treated mice were observed.

Low dose (50mg/kgbw)
The cortex of 50mg/kgbw zidovudine treated group shows edematous changes resulting in spongiform appearance. The cells in the pyramidal layer are showing initial signs of degeneration like shrinkage, irregular chromatin in the nucleus. (figure 3 & 4)

Medium dose (100mg/kgbw)
Severity of changes in the cortex increases. There are considerably large empty lacunar places which are formed due to degeneration of pyramidal cells and edematous changes occurring inside the cortical layer.

There is vast areas showing degenerated pyramidal cells with considerable amount of cellular debris. Pathognomic changes of cell degeneration like pyknotic nuclei, karyolysis and karyorrhexis are well visualized in this group. (figure 5 & 6)

High dose (150mg/kgbw)
In the 150mg/kgbw treated cerebral cortex there is absolute loss of the cyto-architecture and laminar pattern. The six layers of the cortex are porly visualized. Vast areas of degeneration and necrosis of pyramidal cells are seen and there are large vacuolar spaces inside the cerebral cortex.

Prominent cellular debris is scattered in the vacuolar spaces showing the immense amount of neurotoxicity induced by zidovudine. (figure 7 & 8)

Discussion

Zidovudine is the first anti-retroviral agent to be introduced into the market. This drug is regularly used in combination with other antiretroviral agents for the treatment of HIV infection as well as for the prevention of mother to child transmission of the virus.

Zidovudine is a prodrug which is first phosphorylated to zidovudine-monophosphate and then into zidovudine bi and tri phosphate. Zidovudine-monophosphate is found to be toxic to mitochondria and it induces degeneration in mitochondria leading to mitochondrial DNA depletion and hence death[3]. Zidovudine also binds with viral DNA as well as host DNA and prevents its chain elongation. This may also result in cell death of the embryo.

Ewing et al. (2000) observed reduced NADH in cerebral mitochondria of monkey fetuses exposed to 40mg zidovudine per day in utero. Also he observed increased level of SDH and cytochrome-c reductase in the same monkeys. He opined that this anomaly in oxidative phosphorylation enzymes may result in damage to mitochondria of cerebral cortex further resulting in neurodegeneration and neuronal deaths[4].

On histological observation of cerebrum there was a dose dependent degeneration of pyramidal cells, edematous changes leading to spongiform appearance and finally loss of laminar pattern of cerebral cortex.

Thus we can hypothecate that zidovudine, due to its mitochondrial toxicity induces increased oxygen stress which is toxic to the developing embryo especially in high doses. So this drug should be used with caution in pregnancy and any other compounding factor which can further augment the oxygen stress should be taken care of.

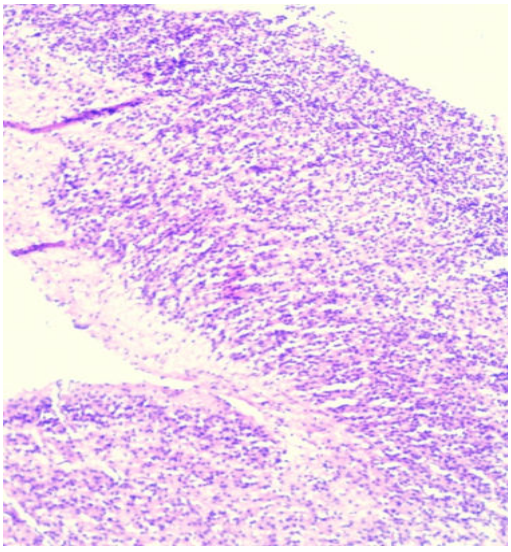

Figure 1: control H&E stained cerebral cortex showing well defined six layers with appreciable pyramidal cells (100X)

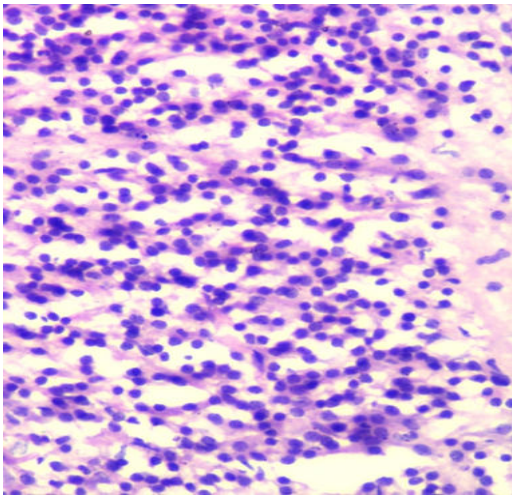

Figure 2: control H&E stained cerebral cortex showing migrating neuroblasts into the cortical plate. (400X).

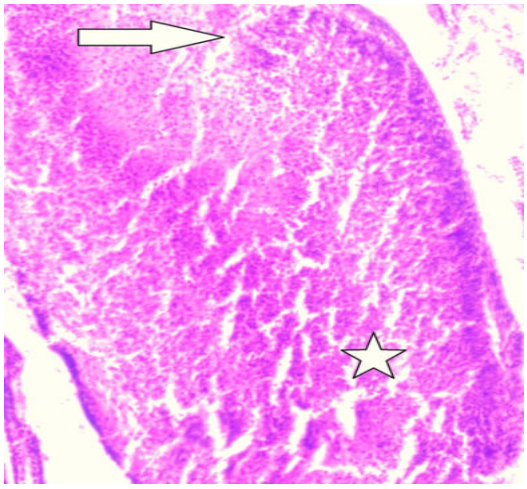

Figure 3: group-2 H&E stained cerebral cortex showing spongiform appearance (*) and cellular degeneration (⟶) (100X)

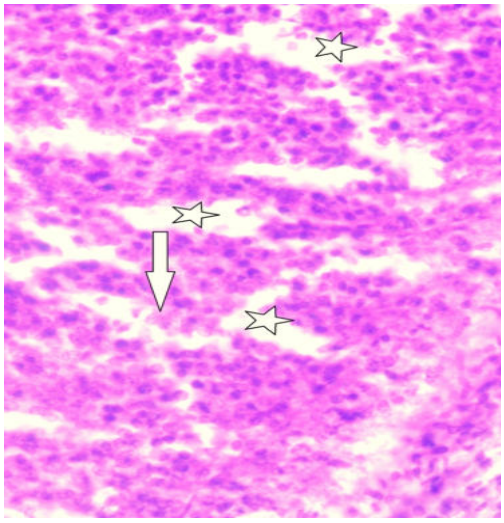

Figure 4: group-2 H&E stained cerebral cortex showing degeneration of neuroblasts (⟶) leading to empty vacuolar spaces (*). (400X)

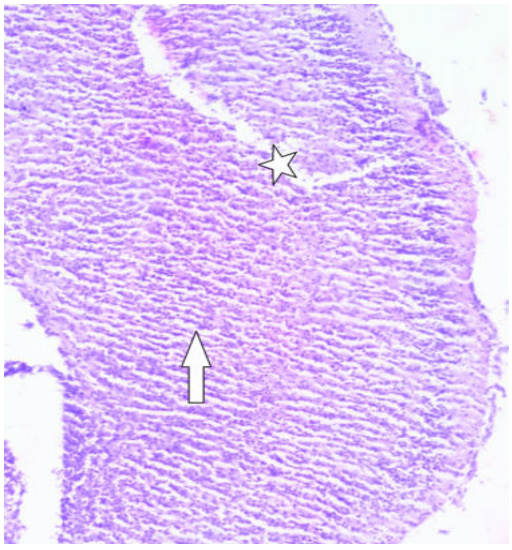

Figure 5 : group-3 H&E stained cerebral cortex showing deficient migration of neuroblasts and its degeneration leading to vacuolar spaces (*) with empty lacunar spaces (⟶). (100X).

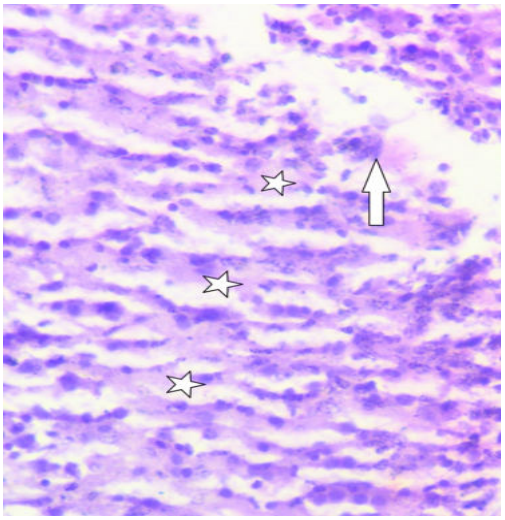

Figure 6 : group-3 H&E stained cerebral cortex showing degeneration of neuroblasts (⟶) with hyaline changes (*). (400X)

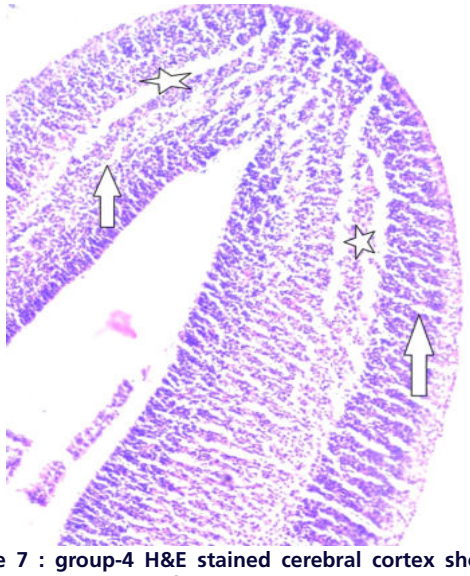

Figure 7 : group-4 H&E stained cerebral cortex showing marked destruction of neuroblasts leading to complete disarray of laminar structure (⟶) with spongiform appearance (*) .(100X)

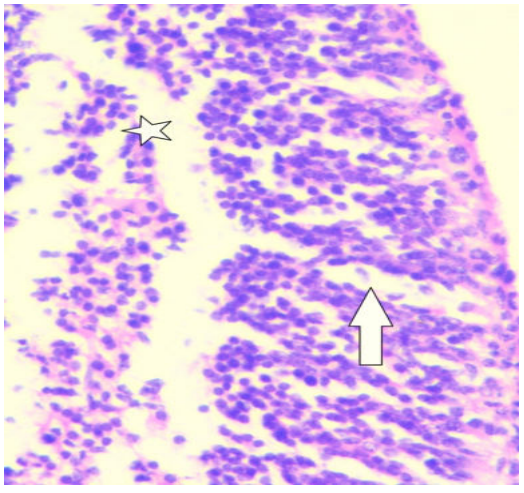

Figure 8: group-4 H&E stained cerebral cortex showing marked destruction of neuroblasts (⟶), cellular debris and complete loss of cytoarchitecture of cerebral cortex (*) (400X)

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