

Identification of Increased Blood Brain Barrier Permeability in the Visual Cortex of the HIV-1 Transgenic Rat

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Significant vision loss has been observed in HIV positive individuals even without infectious retinopathy [1]. For example, highly active antiretroviral therapy (HAART) has resulted in a decrease of opportunistic infections (OI) that affect the retina and brain. One such OI is cytomegalovirus [2] for which there has been a marked decrease. While OIs have decreased, HIV continues to be a problem. It has been established that HIV infects microglia cells. These cells can be found throughout the brain and they are often found in association with endothelial cells. Moreover, these cells are believed to be important viral reservoirs. They can remain infected producing virus and viral proteins even with treatment. Neuropathology can therefore emerge at any location in the brain including the visual system. HIV retinopathy with visual abnormalities has emerged as the most common complication in non-immuno-compromised HIV positive individuals [3]. Therefore, vision loss is becoming a comorbidity associated with HIV infection. [4]. One proposed mechanism for HIV associated neuropathology involves the role of toxic HIV proteins. The reservoir cells continue to produce viral proteins such as HIV-1 envelope protein GP-120. GP-120 may play a key role in Blood Brain Barrier (BBB) dysfunction [9] which can result in increased permeability. Exposure to GP-120 whether acute or chronic leads to leakage of vascular tissues [8] and other pathology [5,6,7]. To further investigate the mechanism of HIV visual loss, we examined the visual system of the HIV- TG rat (HIV-1TGR), a well-established model for the investigation of HIV associated pathologies [10]. Methods: Adult HIV-1 TGRs (N=6) were perfused with buffered formalin. Coronal serial sections were produced including brain cortical areas that include the visual cortex. Alternate sections were immunohistochemically labeled for Rat IgG (a marker of BBB permeability), GFAP (marker for Gliosis) and Nissl Stain (used to established neuroanatomic location). In addition, Senescence Associated Beta-Gal enzyme (SABG) histochemistry was performed on 3 brains using frozen sections (11). Brain locations were determined by comparing them to the rat stereotaxic atlas. Results: Out of 6 brains 2 showed signs of BBB leakage by IgG immunocytochemistry in the visual cortex. As in previous studies SABG staining cells were observed throughout the brain including the visual cortex. The area of increased BBB permeability was also associated with increased Gliosis. Discussion: Our research has found increased IgG labeling in the area of the visual cortex of the HIV-1 TG rat in 2 of the 6 brains. Suggesting breakdown of the BBB. No IgG leakage was observed in controls where labeling was limited to inside the blood vesicles. SABG staining, a marker for premature senescence, was found in cells throughout the brain including the visual cortex in the HIV Tg Rat. Increased labeling for GFAP was found in the visual cortex of one brain. Previous analysis has shown that the GP-120 receptor CXCR4 is present in these brain areas and may provide an explanation for cell death and dysfunction [12]. Further work is underway to investigate the pathology found at all levels the visual system from the retina to the visual cortex.

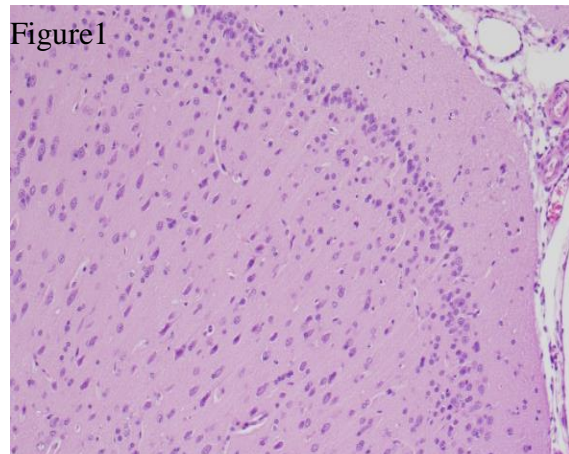


Figure 1. H&E, 10X, HIV-1TG visual cortex

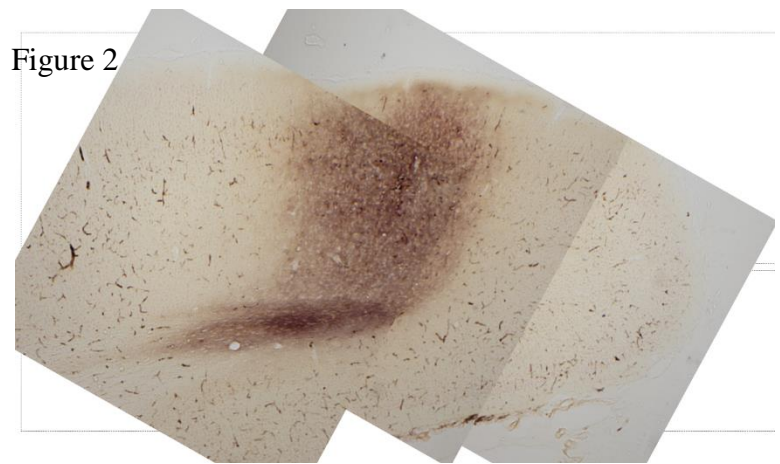


Figure 2. Immunohistochemistry to rat IgG, 10X collage of three adjacent images. Dark brown area demonstrating BBB leakage and permeability.

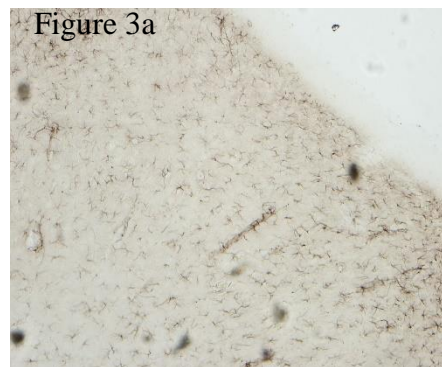


Figure 3a

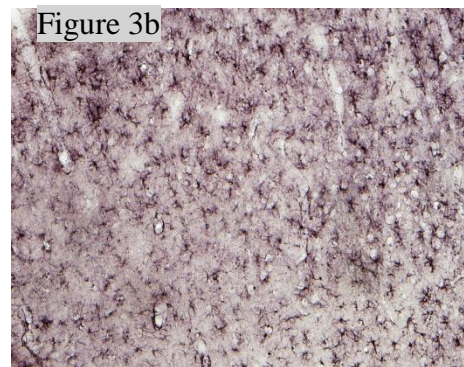


Figure 3b

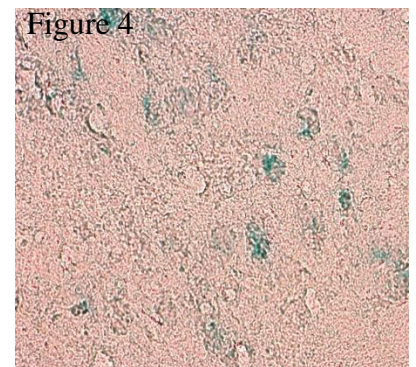


Figure 4

Figure 3a GFAP 10X in Non-HIV-1 TG control. It demonstrates a typical glia distribution pattern.

Figure 3b GFAP 10X in HIV-1 TG Rat. Figure 4 SABG staining 10X, SABG is a marker for premature senescence and is found in the visual cortex.

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