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Neuroinflammation in Asymptomatic HIV-infected Subjects on Effective cART

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Introduction

•Neuroinflammation may contribute to the pathogenesis of HIV-associated neurocognitive impairment

•Positron emission tomography (PET) imaging allows *in vivo* quantification of neuroinflammation by measuring the density of the 18kDA translocator protein (TSPO)

•TSPO is a mitochondrial transmembrane protein highly expressed in microglia

•Following activation microglia increased expression of TSPO. Therefore this can serve as a proxy for microglial activation[1].

•[^{11}C]PBR28 is a second generation TSPO radioligand with high affinity for TSPO that can be used to image microglial activation in the human brain *in vivo* using PET.

• A polymorphism of the TSPO gene (rs6971), results in three different patterns of affinity to [^{11}C]PBR28: low affinity binders (LABs), mixed affinity binders (MABs) an high affinity binders (HABs)

Aim

The aims of the study were:

•To characterise, differences in [^{11}C]PBR28 TSPO binding between HIV-1 infected individuals stable on cART and seronegative controls

•To explore the relationship between [^{11}C] PBR28 TSPO binding and MRI measures of structural and functional brain integrity, cognitive function, and HIV clinical parameters

Methods

•Eligible subjects were HIV-infected, neurologically asymptomatic adults receiving stable combination antiretroviral therapy (cART) with a plasma HIV-RNA <50 copies/mL

•Exclusion criteria included any active or past history of neurological or psychiatric disease, regular use of recreational drugs or alcohol abuse, hepatitis C and being LAB to [^{11}C]PBR28 on genotype testing

•All HIV subjects completed [^{11}C]PBR28 PET CT imaging, neurocognitive testing and cerebral magnetic resonance imaging spectroscopy (^{1}H-MRS) to evaluate *in vivo* cerebral metabolites

[^{11}C]PBR28 PET imaging

•PET scans were acquired using a Biograph 6 PET/CT scanner(Siemens Healthcare)

•A two tissue compartmental model was used to estimate the total volume of distribution (V_T) in regions of interest (ROIs) in each subject

•Individual V_T parametric maps were generated using Logan plot. The distribution volume ratio (DVR) was also estimated by normalizing to cortical grey matter

•Differences between patients and controls were studied both on parametric level using FSL randomise (FMRIB software library) and on ROI (region of interest) level using ANOVA with affinity status as a fixed factor

Methods (continued)

Neurocognitive testing:

•All HIV subjects completed a computerized assessment of cognitive performance (CogState Ltd, Melbourne, Australia) which has been previously validated in this condition[2].

•Scores from each task were obtained and compared against age-matched normative population data provided by the manufacturer. Cognitive impairment was defined as the presence of a cognitive task score below one standard deviation (SD) in at least two cognitive tasks

^{1}H-MRS imaging:

•^{1}H-MRS was performed on a Siemens MAGNETOM Verio 3.0 Tesla scanner at Imanova Centre for Imaging Sciences, London, UK

•^{1}H-MRS data were acquired by single voxel examination in 2 voxel locations: right frontal white matter (FWM) and the right basal ganglia (RBG)

Results

•12 male, HIV subjects (8 HABs and 4 MABs, mean age 42.7± 6.4 years) completed all study procedures

•10 male, healthy, seronegative controls (6 HABs, and 4 MABs, mean age 41.6± 8.6 years) matched by age and ethnicity completed [^{11}C]PBR28 PET CT imaging

Demographic / clinical parameter	Median (range) unless otherwise stated
Ethnicity, n (%)	
White	10 (83.3)
Black	2 (16.7)
Nadir CD4 cell count(cells/uL)	196 (70-350)
Baseline CD4 cell count (cells/uL)	645 (350-1240)
Baseline plasma HIV RNA level<50 copies/ mL, (%)	12 (100)
Pre-ART treatment plasma HIV RNA	128639 (151-1624782)
Years since HIV diagnosis	28 (4)
Years since cART	4 (2-16)
Antiretroviral therapy	15(2-19)
PI based, n(%)	7(58.3)
NNRTI based, n(%)	5(41.7)

***Table 1**:HIV patient demographics and clinical parameters*

Results

•Results of the neurocognitive tests are shown in **Table 2**. No cognitive impairment was observed in the HIV-infected cases compared to the age matched population data

***Table 2:** HIV cases cognitive testing results*

Cognitive function tested , (units)	Interpretation of score (SD)	HIV cases	Age-matched control population[1]
Psychomotor function, (ms)	Lower score=better performance	2.49(0.08)	2.49 (0.09)
Attention, (ms)	Lower score=better performance	2.71(0.64)	2.70(0.07)
Visual Learning, (arcsine proportion correct)	Higher score=better performance	1.06(0.04)	1.01(0.12)
Working memory, (arcsine proportion correct)	Higher score=better performance	1.32(0.07)	1.34(0.19)
Executive function, (total errors)	Lower score=better performance	52.2(13)	55.3(22.42)
Verbal learning, (number of correct responses)	Higher score=better performance	27.2(2)	22.79(5.4)

[1] Age matched control data provided by cogState (n=879)

•Parametric analysis demonstrated a global increase in the mean V_T in HIV cases compared to controls with the most markedly increase in the basal ganglia (BG) after multiple comparisons correction (p=<0.01), see **Figure 1 and 2**

•Significant local increases in DVR in HIV cases compared to controls were found in the parietal cortex (p=<0.01) and globus pallidus (p=0.035) with a significant decrease in DVR in the midbrain (p=0.04) and temporal cortex (p=0.01)

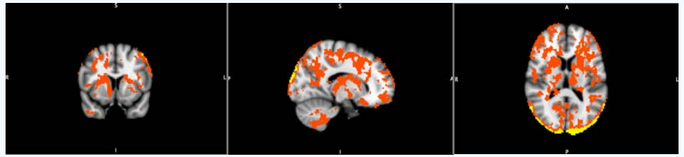
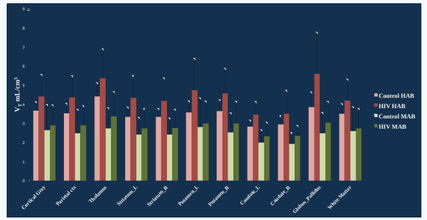


***Figure 1:** Parametric V_T map of brain regions where significant differences in [^{11}C]PBR28 binding between HIV-infected subjects and controls. (significant threshold of P=0.01)*

•In HIV cases, despite cognitive function being intact, after controlling for age and education, greater [^{11}C]PBR28 V_T in the basal ganglia (p=0.018) and parietal cortex (p=0.025) was associated with poorer performance in visual learning and working memory tasks

Results

***Figure 2**: [^{11}C]PBR28 V_T in selected regions of interest investigated for HIV cases and controls. HAB= high affinity binders, MAB: mixed affinity binders*



•Greater [^{11}C]PBR28 V_T in BG was associated with higher pre-treatment plasma HIV-RNA viral load, (p=0.029)

•Associations between V_T in brain regions and other HIV clinical parameters (including, type of cART, nadir CD4 count, years since HIV infection and years since cART, p=>0.1) were not observed.

•Greater [^{11}C]PBR28 V_T was also associated with lower RBG brain myo-inositol/creatine ratio (ml/Cr) a marker of glial inflammation) as evaluated by ^{1}H MRS (p=0.011, r=-0.726)

Conclusion

- In asymptomatic HIV-infected patients a significant increase in microglial activation is present suggesting neuroinflammation despite effective control of HIV plasma viraemia
- Pre-ART treatment plasma HIV-RNA but not nadir CD4 count was associated with increase [^{11}C]PBR28 V_T in the basal ganglia
- We postulate that higher plasma HIV-RNA load during the pre-treatment stages of HIV infection, may lead to persistent microglial activation even after viraemia is controlled with cART
- neuroinflammation was present in brain areas involved with mediating attention and working memory such as basal ganglia, temporal cortex and parietal cortex. These findings suggest that neuroinflammation is implicated in a pre-symptomatic neurological process
- Finally, we observed brain areas with decrease V_T in HIV cases (midbrain and temporal cortex) compared to controls suggesting different microglial/astrocyte activation phenotypes within specific anatomical regions

Summary :

Evidence of neuroinflammation on cerebral PET is present in neuroasymptomatic HIV-infected individuals despite effective control of plasma HIV-RNA and is associated with greater pre-treatment HIV-RNA viral load but not nadir CD4 count

Acknowledgements and References

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