Microbial Translocation is associated with Neuroinflammation in HIV-infected subjects on ART

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Introduction

- Microbial translocation is characterised by the translocation of microbial products derived from the gastrointestinal tract of HIV-infected individuals to the bloodstream.
- Circulating microbial products such as bacterial 16s ribosomal DNA have been associated with chronic immune activation in otherwise effectively treated HIV-infected subjects[1].
- Quantification of bacterial DNA encoding the ribosomal 16s rRNA gene has been proposed as sensitive biomarker of microbial translocation[2]
- The aim of this study was to examine the relationship between a marker of microbial translocation (ribosomal 16s DNA) and brain biomarkers of inflammation, function and structure in treated HIV-infected individuals.

Methods

- Plasma bacterial 16s ribosomal DNA (r16s DNA) was measured by quantitative polymerase chain reaction (qPCR) in 12 neurologically asymptomatic HIV-infected subjects on stable cART with a viral load <50 of copies/mL.
- Brain [11C] PBR28 positron emission tomography (PET) imaging was performed to quantify neuroinflammation in vivo by measuring the density of the 18kDA translocator protein (TSPO), a marker of microglial activation.
- A two tissue compartmental model was used to estimate brain [^{11}C] PBR28 TSPO binding
- Diffusion tensor imaging (DTI) was performed in all HIV-infected subjects.
- Mean FA (fractional anisotropy) and MD (mean diffusivity) in major white matter tracts were calculated by projecting each individual skeleton through masks for the major white matter tracts contained within the JHU white-matter tractography atlas.
- Cerebrospinal fluid (CSF) was obtained from 10 out of 12 HIV-infected subjects.
- CSF chemokines (eotaxin, MIP-1β, and IL-8) were measured by MSD human chemokine-Plex ELISA (Meso Scale Discovery).
- [11C] PBR28 PET CT and DTI imaging data was compared to imaging data from 10 male HIV-negative controls, with a mean age of 41.6± 8.6 years.

Demographic / clinical parameter	Median (range) unless otherwise stated
Ethnicity, n (%) *White* *Black*	 10 (83.3) 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: Clinical parameters of HIV-infected cases

- Associations between plasma ribosomal 16s concentrations, imaging parameters and chemokine concentrations were performed using Pearson or partial correlation analysis adjusted for TSPO affinity status when appropriated.

Results

- Demographics and clinical parameters of HIV-infected cases are presented in Table 1.
- Global increases in PBR28 binding were seen in the brains of HIV-infected subjects compared to HIV-negative controls, ($p<0.01$),Figure 1.

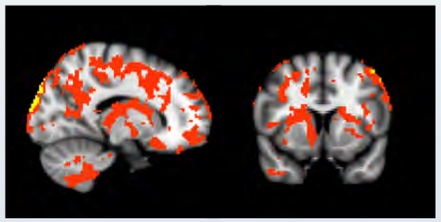


FIGURE 1: Parametric analysis showing significant increase in [11C]PBR28 binding between HIV-infected subjects and controls ($p<0.01$)

- In HIV-infected subjects greater PBR28 binding was found in the globus pallidus ($p=0.035$), basal ganglia and parietal cortex ($p<0.01$) compared to controls.
- A significant increase in MD in the corpus callosum, forceps major, right inferior longitudinal fasciculus and right inferior fronto-occipital fasciculus was observed in HIV-infected individuals compared to controls, ($p<0.01$).
- Plasma ribosomal16s DNA median (range) was 4.2 (41-2) copies/mL.

Biomarker	Basal ganglia	Globus pallidus	Temporal lobe	Parietal lobe	Occipital lobe	Caudate	Striatum	Medulla	Midbrain
Plasma Ribosomal 16s DNA (copies/mL)	0.881*	0.928*	0.818*	0.832*	0.861*	0.877*	0.871*	0.645*	0.811*

*TABLE 2: Correlation coefficients (r) between [11C] PBR28 binding and plasma ribosomal16s DNA. [*P<0.05, ** P<0.1]*

- Significant associations between increase concentration of plasma ribosomal 16s and greater [11C] PBR28 binding were observed across several brain regions. Table 2.

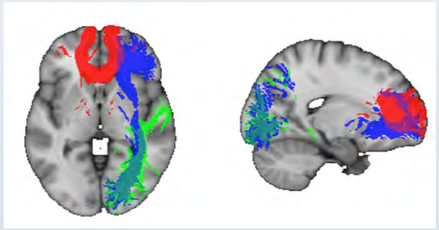


FIGURE 2. Mean diffusivity (MD) map of three brain regions that correlated positively with plasma concentrations of ribosomal 16s; red corresponds to the forceps major, green is the right inferior longitudinal fasciculus and blue is the right inferior fronto-occipital fasciculus.

- Ribosomal 16s DNA was also associated with greater MD in the forceps major (r=0.532; P=0.07), right inferior longitudinal fasciculus (r=0.601; P=0.03) and right inferior fronto-occipital fasciculus (r=0.509; P=0.09). Figure 2.
- Ribosomal 16s DNA level was positively correlated with the proinflammatory chemokine IL-8 in the CSF (r=0.599; P=0.024, CI=0.152 to 0.956).

Conclusions

- In neuroasymptomatic treated HIV-infected individuals microbial translocation is associated with markers of neuroinflammation and abnormalities in white matter integrity.
- We hypothesise that brain immuneactivation might be mediated by peripheral inflammation, caused by the continous release of microbial products from a disrupted gut-blood barrier.
- The potential contribution of microbial translocation to the pathogenesis of HIV-associated cognitive impairment warrants further investigation.

References

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