Subclinical Global and Thalamic Hypometabolism on FDG-PET in Treated HIV+ Subjects

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Introduction

- HIV DNA was identified in > 50% of brain tissues obtained from patients with low or undetectable viral load (VL) in the periphery prior to death[1] suggesting that the CNS harbors latent HIV-1 provirus despite long-term viral suppression by antiretroviral therapy (ART)
- Detectable levels of tat in the CSF of infected patients suggest that the integrated HIV provirus in the brain results in the production of viral proteins [2].
- Both hypo- and hypermetabolic brain abnormalities on [18F]-Fluorodeoxyglucose (FDG) positron emission tomography (PET) were described in the early days of the HIV epidemic however only a few reports evaluated HIV+ patients in the recent ART era.

Project Overview

We imaged a group of optimally-treated HIV+ subjects using 18F-FDG-PET/CT. In order to account for co-morbidities such as cardiovascular disease (CVD) and substance abuse, we compared our HIV+ subjects to two separate HIV-negative groups: one group of subjects that were socio-economically similar to the infected group with multiple co-morbidities (HIV-) and one group of subects with no significant comorbidities (healthy controls, HC).

Methods

Group 1 **(n=47):** HIV+ patients with VL values below the limit of detection in blood for at least one year.

Group 2 **(n=10):** HIV-negative age-matched subjects recruited from the same geographic and socioeconomic areas as the HIV+ group (with multiple co-morbidities).

Group 3 **(n=19):** HIV-negative age-matched healthy subjects with no significant co-morbidities and no history of psychiatric or neurocognitive abnormalities.

A preliminary analysis of whole brain standardized uptake values (SUV) was performed (MIM 6.5 software) using an inclusive volume of interest (VOI) applied automatically around the brain using a threshold-based method, excluding extracranial structures and the pituitary gland (Fig.1). Whole brain VOIs were then analyzed for SUVmean and SUVmax.

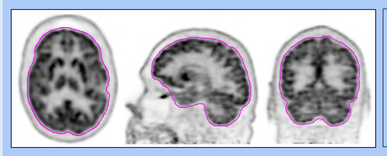

Fig. 1: Whole brain VOI: the caudal border was set at the level of the foramen magnum to maintain consistency of included structures. Minor manual corrections of the borders of the VOI were applied when needed.

For analysis of FDG uptake in subcortical central regions (thalamus, caudate and putamen) and cerebllum, PMOD 3.7 was used. First, automatic template VOIs were applied to the PET scan and those were then manually adjusted as needed. The right and left VOIs were averaged for each subregion and mean SUVs were obtained. Relative SUVmean values were also obtained as follows:

$$\text{Relative SUV mean} = \frac{\text{SUV mean (VOI)}}{\text{Total SUV mean}}$$

Results

Whole brain: HIV+ subjects showed lower SUVmean values compared to HC (p = 0.047) but not compared to HIV- (p = 0.89) subjects. For SUVmax however, group differences were more significant (ANOVA one-way, p = 0.011) with HIV+ showing significantly lower values compared to HC (p = 0.009) (Fig.2).

SUVmean and SUVmax were significantly higher in the HIV+ subjects with no major co-morbidity, compared to HIV+ subjects with one or more major co-morbidity (unpaired t-test, p = 0.039 and 0.031, respectively).

SUVmean and SUVmax were significantly higher in the HIV+ subjects with Atherosclerotic cardiovascular disease (ASCVD) risk scores <7.5 compared to subjects with ASCVD risk scores >7.5% (p = 0.017 and 0.02, respectively).

When the HIV+ and HIV- subjects were evaluated as one group, whole brain SUVmean and SUVmax were best predicted by ASCVD risk scores.

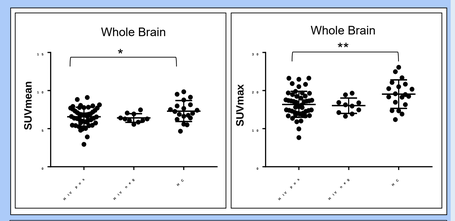

Fig. 2: Scatter plots of whole brain SUVmean and SUVmax in HIV+, HIV- and healthy controls.

Thalamus: significant differences were found between SUVmean and relative SUVmean values in the three groups (one-way ANOVA, p < 0.0001 for both). Thalamic SUVmean values were significantly lower in the HIV+ than the HC group (p = 0.0001) but not the HIV- group (p = 0.73). The relative thalamic SUVmean values, however, were significantly lower in the HIV+ compared to HIV- (p = 0.02) and HC (p = 0.0001) subjects (Fig.3).

Caudate and cerebellum: SUVmean was significantly lower in HIV+ compared to HC group (p = 0.004). The HIV- group values were not significantly different from HIV+ values. Relative SUVmean however were not significantly different among groups (Fig.3).
Putamen: no significant differences were seen between the SUVmean or relative SUVmean values of the three groups (Fig.3).

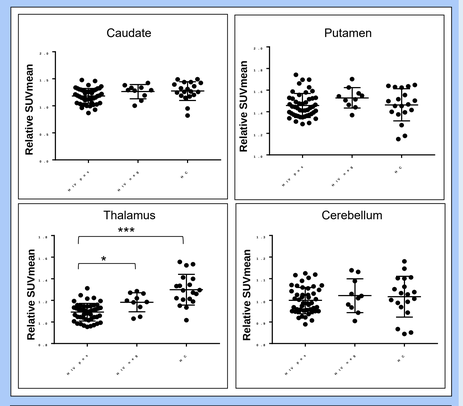

Fig. 3: Scatter plots of relative SUVmean values for the caudate, thalamus, putamen and cerebellum in HIV+, HIV- and healthy controls.

In some HIV+ patients, thalamic hypometabolism could be detected visually, when compared to nearby caudate and putamen metabolism (figures 4 and 5). 3D-rendered projections of the entirety of the basal ganglia and thalami better show those findings.

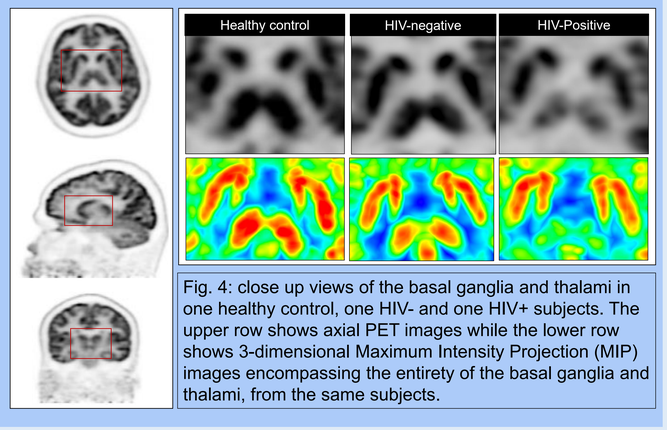

Fig. 4: close up views of the basal ganglia and thalami in one healthy control, one HIV- and one HIV+ subjects. The upper row shows axial PET images while the lower row shows 3-dimensional Maximum Intensity Projection (MIP) images encompassing the entirety of the basal ganglia and thalami, from the same subjects.

Results

When HIV+ and HIV- subjects were evaluated together, relative SUVmean values in the thalamus were best predicted by a combination of HIV status (p = 0.01) and ASCVD risk scores (p = 0.0025). This was followed by prior drug use (p = 0.011).

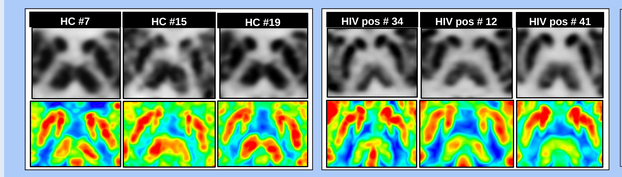

Fig.5: Additional examples of visually detectable thalamic hypo-metabolism in HIV+ subjects compared to healthy controls

Correlation with neuropsychiatric (NP) tests: There were no significant correlations identified between the major NP test results (GDS, overall T scores and HAND diagnosis) and whole brain SUVmean, whole brain SUVmax, regional SUV mean or regional relative SUVmean values.

Conclusions

When HIV+ and HIV- subjects were evaluated as one group, ASCVD risk scores rather than HIV status were most predictive of whole brain SUVmean and SUVmax, emphasizing the importance of cardiovascular disease on brain metabolism. **Our findings underscore the impact of cardiovascular disease in this vulnerable patient population and the importance of better screening and control strategies to halt the potential associated neurocognitive decline.**

Besides co-morbidities however, at least one area in the brain, the thalamus, seems to have more significant damage in HIV+ subjects compared to HIV- subjects suggesting a possible role of the virus. When evaluating group 1 and group 2 together, the relative thalamic SUVmean values were best predicted by a combination of HIV status and ASCVD risk scores.

The thalamus is considered a major relay center of somatosensory spinal, cranial nerve, visual, auditory, basal ganglia and cerebellar inputs to the cortex and a main subcortical component of arousal and alertness. **Our findings of thalamic hypometabolism in HIV+ subjects could potentially explain subtle abnormalities noted in this patient population for the domains of concentration, attention, memory and impaired executive function.**

Our results are consistent with previous volumetric MR imaging studies which described thalamic involvement in ART-treated patients [3-6] suggesting virus related effect. The implications of those findings are unclear, however they open the door to a more serious discussion about neurocognitive abnormalities still prevalent in HIV+ subjects despite treatment and virological suppression, both in the periphery and in the brain.

References

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