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Original Article

Hippocampal MR spectroscopic abnormalities in a cohort of syphilitic patients with HIV and neurosyphilis infection

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Abstract: Co-infection of human immunodeficiency virus (HIV) and neurosyphilis (NS) has become a rising trend, but the extent of brain damage associated with the concomitant infections remains unknown. Proton magnetic resonance spectroscopy (^{1}H-MRS) can evaluate metabolic changes underlying early brain infections. 25 syphilitic patients (7 HIV-positive with NS; 6 HIV-positive without NS; 5 HIV-negative with NS; 7 non-HIV, non-NS) and 17 healthy controls (HC) underwent single-voxel ^{1}H-MRS in the bilateral hippocampi. Absolute concentrations of major metabolites were measured using a 3T MRI scanner. No significant structural abnormality was detected in all patients. However, metabolic changes were found in the left hippocampus of both the HIV-positive and NS subgroups, showing significantly higher choline (Cho), creatine (Cr) and myo-inositol (mI) compared to HC. In the right hippocampus, HIV-positive subgroup showed significantly higher Cr and reduced NAA, while NS subgroup only showed significantly reduced NAA compared to HC. The non-HIV, non-NS syphilitic subgroup showed no significant difference compared to HC. Substantial metabolic changes occurred in bilateral hippocampi in HIV and NS co-infections. NAA reduction might represent early neuronal damage, while mI/Cho elevation reflects gliosis/inflammatory changes. ^{1}H-MRS could serve as a non-invasive tool to triage patients suspected of NS for lumbar puncture in non-HIV syphilitic patients.

Keywords: HIV, neurosyphilis, co-infection, magnetic resonance spectroscopy, hippocampus

Introduction

Central nervous system (CNS) is commonly involved in the early stage of human immunodeficiency virus (HIV) infection. HIV can invade the brain directly, involving the glial cells and neurons, causing subclinical encephalitis [1-3]. After the onset of acquired immune deficiency syndrome (AIDS), approximately 10-15% of the AIDS patients will develop HIV-associated dementia complex, characterized by cognitive, behavioral, and motor dysfunction [4]. The early initiation of antiretroviral therapy reduced rates of sexual transmission of HIV and clinical events such as early occurrence of pulmonary tuberculosis, severe bacterial infection or death [5]. However, with the advent of highly active antiretroviral therapy (HAART), rates of syphilis and other sexually transmitted diseases (STDs) have risen among men who have sex with men (MSM), reflecting a general increase in unsafe sexual behavior [6, 7].

Another common sexually transmitted disease (STD) with CNS invasion is neurosyphilis (NS), being caused by the spirochete *Treponema pallidum*. About 1/3 of patient with early syphilis have invasion of the treponemes in the cerebrospinal fluid (CSF), regardless of their HIV status [7]. There is no single reliable diagnosis of NS due to a lack of infallible laboratory test, obscurity in clinical symptoms and the possibility of giving both false positive and false negative results in CSF-Venereal Disease Research Laboratory (CSF-VDRL) test [8-10].

The increased occurrence of NS with HIV infection has been reported in previous studies [11-

14]. The reported prevalence of NS in HIV infected patients can be as high as 23.5-40%, compared to 10% in HIV seronegative patients with untreated syphilis. Co-infection with NS in HIV patients has adverse effects on clinical outcome and prognosis [15]. Complex interactions between HIV and NS had been reported, impacting clinical manifestations, diagnosis, and treatment of syphilis [7, 16]. Some studies suggested that HIV-related immunocompromise has the potential to promote syphilitic involvement of the CNS [6, 7, 17, 18]. In addition, disorder of the humoral immune response to *Treponema pallidum* in HIV patients can produce confusing results in serological tests for NS [18, 19]. Nevertheless, one recent study [20] showed that under HAART treatment, the effect of HIV on serologic response to syphilis treatment was likely minimal or absent.

Up-to-date, there was only one neuroimaging study on HIV positive (HIV+) and HIV negative (HIV-) patients with NS [12], though no comparison can be made due to the limited number of only 3 HIV- NS patients in contrast to 32 HIV+ NS patients. The authors suggested that presence of vascular occlusive disease in HIV+ patients should prompt the appropriate testing for NS.

There are recent retrospective reports on Magnetic Resonance Imaging (MRI) findings of brain in NS patients, including T2 hyperintensity in mesial temporal lobes and other less specific regions, and atrophy especially in temporal and frontal lobes [21-24]. In particular, some studies reported resolution of T2 hyperintensity after treatment for NS [22, 24]. The pathological basis of such changes in MRI brain remains to be confirmed.

Interestingly, viral loads of HIV had been reported to be particularly high in the hippocampus [25]. A prior functional MRI (fMRI) study revealed that compared to HIV- women, HIV+ women showed decreased activation during encoding, and increased activation during recognition in bilateral hippocampi in a delayed verbal episodic memory task, suggesting HIV might affect the functional integrity of the medial temporal system [26]. Another fMRI study of well-educated HIV+ men demonstrated reduced signal intensity in right posterior hippocampus and right inferior frontal gyrus, during encoding of scenes [27]. All these findings suggested HIV functionally impacted the hippocampal system.

Proton magnetic resonance spectroscopy (^{1}H-MRS) can measure metabolite levels by using proton signals from the metabolites and has been employed extensively in HIV infection. A summary of these studies was tabulated in **Table 1**. Many studies found lowered N-acetyl-aspartate/creatine (NAA/Cr), or N-acetyl-aspartate/choline (NAA/Cho) or both in the subcortical white matter of asymptomatic HIV+ patients [28-30], and in AIDS dementia complex (ADC) patients [1, 28, 31-33]. These reductions might represent early neuronal damage without gross anatomical abnormalities. Other studies using absolute quantification also confirmed lower absolute concentrations of NAA in the white matter of ADC [34], HIV+ patients with cognitive impairment [35], asymptomatic chronic HIV+ [36], and in the basal ganglia of HIV dementia [37]. Interestingly, a recent ^{1}H-MRS study using absolute quantification reported that NAA and Glx (glutamine plus glutamate) concentrations were significantly reduced in the cortical gray matter of early HIV-infected subjects, but not in the deep white matter, further indicating HIV might cause neuronal dysfunction after infection [36].

Prior studies also reported elevated myo-inositol (mI) or mI/Cr level in frontal white matter and/or basal ganglia of HIV-associated dementia patients [1, 31, 33, 37]. These elevations might be due to increased glial activity. Another metabolite which is also related to glial cells is choline (Cho). In previous studies in asymptomatic HIV patients, deep white matter Cho or Cho/Cr level was found to be increased [30, 35, 38] or have no change [28, 29], while elevated Cho or Cho/Cr was seen in the ADC stage [1, 28, 33-35, 38]. Elevated Cho might be explained by cellular injury and glial proliferation as higher concentration of Cho was found in glial cells [39].

Although ^{1}H-MRS may serve as a noninvasive mean of determining neuronal injury and neurologic dysfunction in HIV patients, and monitoring of HAART [40, 41], there is a paucity of literature on ^{1}H-MRS study in NS. Hence, the potential role of ^{1}H-MRS in NS remains to be elucidated, such as detection of any early brain injury or assessment of treatment response of NS in HIV patients (since confusing results in serological tests might occur in these patients).

Table 1. Summary of previous studies using proton magnetic resonance spectroscopy (^{1}H-MRS) to measure metabolite levels in HIV infection

Study	Title/Purpose	Methodology (sample size/region-of-interest/ quantification method)	Results
[1]	Clinical severity of HIV-1 cognitive motor complex	20 HIV-MCMD, 34 HIV-dementia, 29 HC/Frontal cortex, frontal white matter, basal ganglia/Absolute (corrected for CSF)	3 groups differ in mI, Cho in frontal WM HIV-CMC: ↑mI and ↑Cho with ↑ADC stage and ↓NAA in moderate to severe ADC stage CD4 count, CSF viral load correlate with metabolites HIV-dementia scale correlate with metabolites ↓NAA/Cr in frontal WM of early HIV-CMC due to slight but non-sig ↑Cr with slight ↓NAA
[28]	HIV-related metabolic abnormalities in the brain	12 ADC, 11 HIV+ asymptomatic, 10 HC/Parietooccipital, bioccipital/Ratio	ADC- brain atrophy and diffuse white matter, ADC vs HC: ↓NA/Cr, ↑mI/Cr, ↑Cho/Cr HIV+ vs HC: ↓NA/Cr, ↑mI/Cr , no change Cho/Cr
[29]	Neurologically asymptomatic HIV-infected patients	30 asymptomatic HIV, 13 HC/Centrum semiovale (both sides) & thalamus/Ratio	↓NAA/Cr & ↓NAA/Cho in centrum semiovale and thalami ↓NAA/Cr more in WM than GM trend towards correlation between CD4 and NAA/Cr
[30]	Neurologically asymptomatic HIV-infected patients	20 asymptomatic HIV, 32 HC/Frontal lobe WM/Ratio	HIV+: ↓NAA/Cho, ↓NAA/H_2O & Cr/H_2O ; ↑Cho/Cr & mI/Cr significant correlation of CD4 and NAA/H_2O
[31]	Multi-centre study of two MRS techniques in individuals with HIV dementia	20 HIV+, 3 HIV- HC/Frontal WM (SVS), mesial frontal GM (MRSI)/Ratio	HIV+ with psychomotor slowing compared to HIV+ without psychomotor slowing: ↑mI/Cr in frontal WM (SVS), ↑Cho/Cr in mesial frontal GM (MRSI) HIV+ with dementia compared to HIV+ without dementia: ↓NAA/Cho in mesial frontal GM (MRSI)
[32]	HIV-infected individuals	7 ADC, 8 HIV+, 7 HC/Frontal WM and GM/Ratio	HIV+ vs HC: ↑mI/Cr in WM ADC vs HC/HIV+: ↓NAA/Cr in GM Correlation with neuropsychiatric tests: poor neuropsychiatric performance with ↓NAA/Cr in GM & WM poor neuropsychiatric performance with ↑mI/Cr in WM
[33]	AIDS Dementia Complex:	38 ADC, 18 HC/Midline posterior parietal cortex (GM), mid frontal CS (WM), basal ganglia (GM)/Ratio	ADC vs HC: ↓NAA/Cr in frontal WM, not parietal GM ADC vs HC: ↑Cho/Cr & ↑mI/Cr in basal ganglia and WM
[34]	AIDS Dementia Complex	7 ADC, 7 HC/11 regions (CSF contamination in caudate)/ Absolute (arbitrary unit)	↓NAA, ↑Cho in WM
[35]	Cognitively and clinically asymptomatic HIV patients	70 HIV+ (varying severities), 30 HC/2 caudate, 2 lenticular nuclei, 2 thalami/Absolute	HIV+: ↑subcortical Cho, ↓subcortical NAA only in cognitively impaired HIV+ subcortical NAA correlate with neuropsychiatric but not CDC stage high thalamic Cho associated with ↓CD4
[36]	Early HIV infection	8 early HIV, 9 HC, 10 chronically HIV-infected asymptomatic/Superior frontal GM, centrum semiovale WM/ Absolute	↓NAA & ↓Glx cortical gray matter of HIV+ subjects ↓NAA centrum semiovale of chronic HIV+ ↓NAA frontal cortex with early infection associated with ↑CD8
[37]	Brain metabolism & cognitive impairment in HIV infection:	86 asymptomatic HIV: 21 normal cognition, 31 MCI, 34 HAD/Frontal WM & basal ganglia/Ratio	Frontal WM Glx & Glx/Cr↓ in HAD vs MCI/NC Frontal WM mI & mI/Cr↑ in HAD vs MCI/NC Basal ganglia NAA↓ in HAD vs MCI/NC Significant correlation between Glu/Glx, NAA with neuropsychiatric tests
[38]	HIV+ patients before the onset of AIDS dementia complex	20 HIV+ (varying stages of ADC), 10 HC/GM precuneus, both hemispheres/Ratio	↓NAA/Cr with advanced dementia ↑Cho/Cr with early HIV infection or CD4>200/μl ↑Cho before ↓NAA, before MRI abnormalities and dementia onset
[40]	HAART reverses brain metabolite abnormalities in mild HIV dementia	16 HIV-CMC (before & after HAART), 15 HC/Frontal lobe (GM & WM), basal ganglia/Absolute and Ratio	Reversal of ↑Cho/Cr in midfrontal cortex by 8.0%, basal ganglia by 14.7% Reversal of ↑mI/Cr & mI in basal ganglia by 14.1% & 11.8% respectively Normalization of mI in frontal WM, change of mI correlate with CD4 (r=-0.67), and ADC stage
[41]	Change in brain MRS after treatment during acute HIV infection	31 acute HIV+, 26 chronic HIV+, 10 HIV- HC/Left frontal WM, basal ganglia, midline FGM, occipital GM/Ratio	acute HIV vs HC/chronic HIV: ↑Cho/Cr in basal ganglia and occipital GM

Key: ADC, AIDS dementia complex; Cho, choline; Cr, creatine; Glx, glutamate and glutamine complex; GM, grey matter; HAART, highly active antiretroviral therapy; HAD, HIV-associated dementia; HC, healthy control; HIV-CMC, HIV-cognitive motor complex; HIV-MCMD, HIV-minor cognitive motor disorder; MCI; mild cognitively impaired; mI, myo-inositol; MRSI, magnetic resonance spectroscopic imaging; NA, N-acetyl compounds; NAA, N-acetyl-aspartate; NC, normal cognition; SVS, single-voxel spectroscopy; WM, white matter; ↑, significant increase; ↓, significant decrease.

Table 2. Clinical profiles of syphilitic patients recruited from local sexual health clinics

Patient (Sex/Age/clinical features)	HIV status [Duration between Diagnosis of HIV and MR scan]	NS status	CD4 cell count (μL)	Viral Load (copies/ml)	Syphilis stage (Duration of treatment for known stage of syphilis between start of treatment and MRI scan)
1 (M/38)	Positive [2 years]	Negative	237	<75 (on HARRT for 1.5 years)	Early latent (not on treatment)
2 (M/28/genital warts)	Positive [1 month]	Positive	493	37000	NS (not on treatment)
3 (M/61)	Positive [1 month]	Positive	243	36000	NS (not on treatment)
4 (M/60)	Positive [2 months]	Positive	436	270000	NS (on treatment for 1 month)
5 (M/60)	Positive [4 months]	Negative	184	320000	Late latent (on treatment for 2 months)
6 (M/24)	Positive [1 month]	Positive	320	110000	NS (not on treatment)
7 (M/42)	Positive [20 years]	Positive	985	<75 (on HARRT for 13 years)	NS (not on treatment)
8 (M/47)	Positive [<1 month]	Negative	258	45000	Late latent (not on treatment)
9 (M/38/genital warts)	Positive [1 month]	Positive	222	290000	NS (not on treatment)
10 (M/47)	Positive [2 months]	Negative	58	790000 (on HARRT for 7 days)	Late latent (not on treatment)
11 (M/29)	Positive [2 months]	Negative	227	150000	Secondary (not on treatment)
12 (M/32)	Positive [1 month]	Negative	385	34000	Late latent (not on treatment)
13 (M/43)	Positive [3 months]	Positive	325	180000	NS (not on treatment)
14 (M/59/raised VDRL titer after treatment)	Negative	Positive	-	-	NS (on treatment for 1 month)
15 (F/55/nonspecific genital infection, right intermediate uveitis)	Negative	Positive	-	-	NS (on treatment for 13 months)
16 (M/50/bilateral scleritis)	Negative	Positive	-	-	NS (not on treatment)
17 (M/62/uveitis)	Negative	Positive	-	-	NS (not on treatment)
18 (M/64/dementia)	Negative	Positive	-	-	NS (on treatment for 2 months)
19 (F/35/right vitritis)	Negative	Negative	-	-	Late latent (not on treatment)
20 (M/66/sensorineural hearing loss)	Negative	Negative	-	-	Late latent (not on treatment)
21 (F/68/persistent high titer VDRL after treatment)	Negative	Negative	-	-	Late latent (on treatment for 13 months)
22 (F/59/bilateral anterior uveitis)	Negative	Negative	-	-	Late latent (not on treatment)
23 (M/69/right optic neuritis)	Negative	Negative	-	-	Late latent (on treatment for 8 months)
24 (F/60/uveitis)	Negative	Negative	-	-	Late latent (not on treatment)
25 (M/58/bilateral optic atrophy, gonorrhea)	Negative	Negative	-	-	Late latent (not on treatment)

In this study, we evaluated a cohort of syphilitic patients referred from several sexual health clinics, suspected of NS due to positive VDRL titer after treatment, HIV status or neurological manifestations. We attempted 1) to detect early metabolic changes in the hippocampi of HIV+, NS positive (NS+) and non-HIV, non-NS patient subgroups, and 2) to evaluate the potential role of ^{1}H-MRS in detecting NS in patients with reactive syphilis serology, with and without co-infection with HIV.

Methods

Subjects

Twenty-seven syphilitic serology positive patients with indications for lumbar puncture (i.e. neurological manifestations, co-infection with HIV, or persistently raised VDRL titer after treatment) and consented to have MRI done, were recruited from several sexual health clinics during the period from December 2010 to October 2012. All patients were scanned within two months (range- 2 to 57 days) after the lumbar puncture.

The clinical profiles of the syphilitic patients were listed in **Table 2** (except 2 patients in Group C). In this cohort of 25 syphilitic patients, there were 12 patients with NS, 11 with late latent, 1 with early latent and 1 with secondary syphilis.

Group A: There were 13 male HIV+ patients (mean age: 42.23±12.52 years; 7 with NS and 6 without NS). HIV+ patients were identified by two subsequent enzyme-linked immunoassay (ELISA) tests and confirmed with Western Blot. Their plasma viral loads and CD4 cell counts were tabulated in **Table 2**. Three out of the thirteen HIV+ patients were receiving HAART, and one of them for less than 7 days.

Group B: There were 12 NS+ patients (mean age: 48.83±13.71 years; 7 with HIV and 5 without HIV). The diagnosis was made strictly according to the 2010 Sexually Transmitted Diseases Treatment Guidelines by the Centers for Disease Control and Prevention (CDC) [42]. Four patients were under treatment of NS at time of MRI scanning; 3 for 2 months or less, and 1 for 13 months.

Group C: There were 9 patients who were negative for both HIV and NS. One patient had dementia and one had poor-quality MR spectra, and both were excluded in the ^{1}H-MRS data analysis. Hence, only 7 patients with mean age of 59.29±11.60 years were included in this group. They were all late latent cases and only 2 had been treated at time of MRI scanning.

17 healthy controls (Group D) with mean age of 39.59±13.87 years were recruited from the university staff and students. They were screened and excluded for high systolic blood pressure (>140 mmHg), previous cerebrovascular events and claustrophobia. They did not have any history of neurological disease and were not taking any psychiatric drug. They attended the university health clinic for routine check-up, which included blood pressure checking as well as clinical and physical examination by a registered medical practitioner. No memory deficit was detected on assessment.

All patients and healthy controls gave their informed consent to participate and the study was approved by the local Institutional Review Board.

Data acquisition

All MR scans were performed using a 3T scanner (Achieva 2.6.3, Philips Healthcare, Best, The Netherlands). A sensitivity encoding (SENSE)-head-8-coil, was used.

MRI: A standardized T1W 3D volumetric Fast Field Echo (FFE) sequence was employed with the following imaging parameters: repetition time TR/TE=7.0/3.2 ms, voxel size=1 x 1 x 1mm^3, field of view (FOV)=256 x 256 x 167 mm^3, reconstruction matrix=256, turbo field echo (TFE) factor=240. Images acquired from T1W 3D FFE were employed for the positioning of single-voxel-spectroscopy (SVS) for ^{1}H-MRS. Axial T2-weighted fast spin-echo images (TR/TE=3000/80 ms, flip angle 90°, slice thickness 5 mm, ETL 16) and T2-weighted fluid-attenuated inversion-recovery (FLAIR) fast spin-echo images (TR/TE=11000/120 ms, slice thickness 2.5 mm, reconstruction matrix 512) were also acquired to exclude structural abnormalities. T1 and T2 images were interpreted by an experienced neuroradiologist (HKFM), who was blinded to the HIV and NS status of the patients. Susceptibility weighted images (SWI) were obtained using 2 mm slice thickness, FOV=230 x 201 x 135 mm^3, TR/TE=28/23 ms. Magnetic

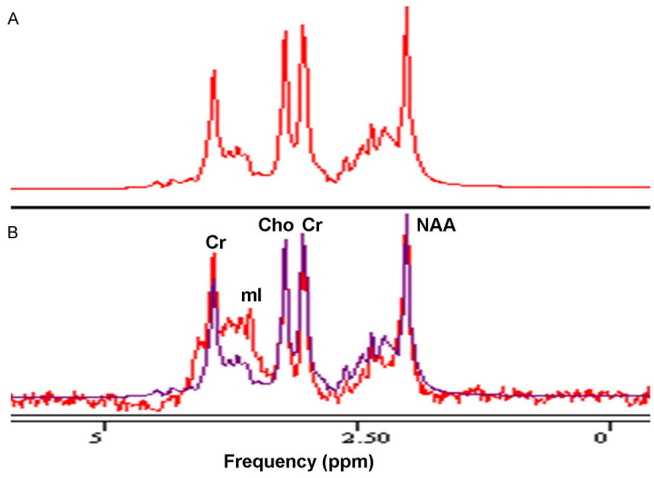

Figure 1. Example of spectra in jMRUI of a 29-year-old HIV+ without NS subject's left hippocampus, simulated spectrum using QUEST (A), spectrum obtained from the subject (red) superimposed on the simulated spectrum (blue) from QUEST (B).

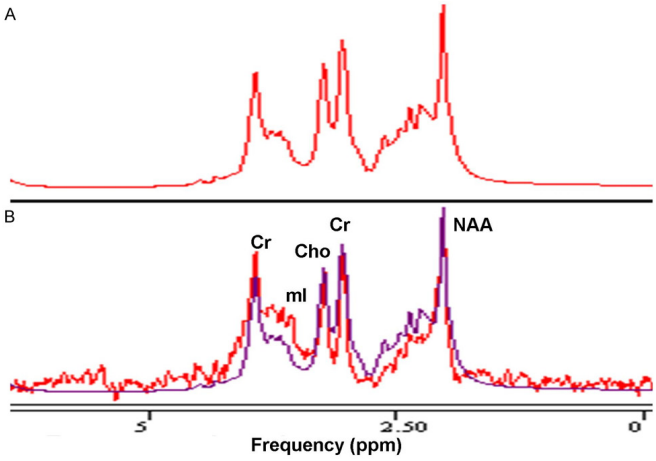

Figure 2. Example of spectra in jMRUI of a 25-year-old healthy control's left hippocampus, simulated spectrum using QUEST (A), spectrum obtained from the subject (red) superimposed on the simulated spectrum (blue) from QUEST (B).

resonance angiography (MRA) was also performed using 2.5 mm slice thickness, FOV=230 x 201 x 137 mm^3, TR/TE=11000/230ms, inversion time=2800ms and flip angle 20°.

^{1}H-MRS: Point resolved spectroscopy (PRESS) was used as the volume selection method for the region-of-interest (ROI) and excitation for water suppression. Scanning parameters are: TR/TE=2000/39 ms, number of signals averaged (NSA)=128, phase cycles=16, spectral width=2000 Hz with spectral resolution of 1.95 Hz per point, free induction decay=1024. For shimming, pencil-beam-auto was employed. Voxels of size 2.5 x 1.5 x 1 cm^3 were placed in the left and right hippocampi. The whole scan time was approximately 60 minutes.

Data analysis

MRI: T2-weighted and FLAIR images were interpreted by an experienced neuroradiologist (HKFM), with scores based on the semi-quantitative Fazekas-scale [43]. SWI and MRA were also interpreted to look for hemorrhages and vascular stenosis respectively. Cortical atrophy was determined by visual inspection [12].

^{1}H-MRS: In this study, two ^{1}H-MRS files were generated simultaneously by our scanner. One file was the actual (suppressed) ^{1}H-MRS data, the other file was the unsuppressed water signal intensity ^{1}H-MRS file. For our absolute concentration calculation, the unsuppressed water signal intensity was used as internal reference.

The ^{1}H-MRS spectra were processed with an offline java-based version of jMRUI (4.0) software. Spectrum simulation of various metabolites was completed using the built-in NMR-SCOPE. Signal amplitudes were determined using QUEST (quantification based on quantum estimation). The unsuppressed water signal was also measured using jMRUI. Cho, Cr, ml and NAA were measured and quantified as described in a previous study [44]. Examples of spectra in jMRUI of a HIV+ patient and a healthy control were illustrated in **Figures 1** and **2** respectively.

Image processing: In order to account for the variations in water content in gray matter (GM), white matter (WM) and CSF, Voxel-Based Morphometry (VBM) was used to determine the GM, WM and CSF composition within the voxel of each of the two regions investigated, as detailed in our previous publications [44, 45].

Statistical analysis: SPSS 20.0 was employed for statistical analysis. Two-samples t-test was used to compare the metabolite concentrations and metabolic ratios between Groups A, B and C with normal controls (Group D). Since Groups C and D differed significantly in age,

Table 3. MRI findings of syphilitic patients recruited from local sexual health clinics

Patient (Sex/Age)	T_2/FLAIR scores and Hyper-intensity	Cerebral infarcts	Cortical atrophy	Hemorrhage
1 (M/38)	1 Punctate few	Nil	Nil	Nil
2 (M/28)	0 Nil	Nil	Nil	Nil
3 (M/61)	1 Few punctate	Nil	Mild	Nil
4 (M/60)	1 Few punctate	Nil	Minimal to mild	Nil
5 (M/60)	1 Multiple punctate	Nil	Moderate	Nil
6 (M/24)	0 Nil	Nil	Nil	Nil
7 (M/42)	0 Nil	Nil	Nil	Nil
8 (M/47)	0 Nil	Nil	Minimal	Nil
9 (M/38)	0 Nil	Nil	Minimal	Nil
10 (M/47)	1 Scattered punctate	Nil	Minimal	Nil
11 (M/29)	1 Few punctate	Nil	Nil	Nil
12 (M/32)	1 Few punctate	Nil	Nil	Nil
13 (M/43)	1 Few punctate	Nil	Nil	Nil
14 (M/59)	1 Few punctate	Nil	Nil	Nil
15 (F/55)	0 Nil	Nil	Nil	Nil
16 (M/50)	0 Nil	Nil	Mild	Nil
17 (M/62)	0 Nil	Nil	Nil	Nil
18 (M/64)	3 Multiple punctate and confluent	Nil	Marked	Nil
19 (F/35)	0 Nil	Nil	Nil	Nil
20 (M/66)	2 Punctate and early confluent	Bilateral centrum semiovale, pons	moderate to severe	Nil
21 (F/68)	1 Multiple punctate	Nil	Mild to moderate	Cavernomas
22 (F/59)	2 Punctate and early confluent	Left insula, bilateral putamen	Minimal	Microbleeds
23 (M/69)	1 Scattered punctate	Nil	Mild	Left cerebellar vascular malformation
24 (F/60)	1 Scattered punctate	Nil	Minimal	Nil
25 (M/58)	1 Scattered punctate	Nil	Mild	Scattered microbleeds

age was adjusted using a linear regression model. The level of significance was set at 0.05.

Results

Immunologic data

The immunologic data of the HIV+ patients were tabulated in **Table 2**. HIV+ patients had a median CD4 cell count of 258 cells/uL and median plasma viral load of 110,000 copies/ml. Of all the thirteen HIV+ patients, three patients were receiving HAART. One patient just started HAART for less than 7 days had plasma viral load of 790,000 copies/ml and CD4 count of 58 cells/uL. Other two patients who were both receiving HAART for more than 1.5 years had undetectable viral load levels (<75 copies/ml) and an average CD4 cell count of 611 cells/uL. In view of limited sample size, correlative study between immunologic data and metabolite levels was not performed.

MRI findings of patients from sexual health clinics

The MRI findings of the patients were tabulated in **Table 3**. The structural images of all patients did not reveal any cerebral infarct (except 2 patients in Group C), and showed only non-specific punctate T_2/FLAIR signal abnormalities in the subcortical and deep white matter of the cerebral hemispheres (Fazekas' score- 0 or 1). 1 patient in Group B and 2 patients in group C had confluent signal abnormalities (Fazekas' score- 2 or 3). Only 3 patients showed moderate to marked cortical atrophy, with 1 patient from each patient group. None of the patients showed arteritis in MRA.

^{1}H-MRS

The mean absolute metabolite concentrations and metabolite ratios of the healthy controls, HIV+ patients, NS+ patients and non-HIV, non-NS patients were tabulated in **Table 4**.

Mean absolute concentrations of metabolites and metabolite ratios in HIV+ patients

In the left hippocampus, HIV+ patients showed significantly higher Cho (p=0.023), Cr (p=0.018) and mI (p=0.005) compared to normal controls. In the right hippocampus, HIV+ patients showed significantly higher Cr (p=0.029), lower

Table 4. Mean concentrations and ratios of various metabolites showing statistical results between different cohorts

		[Cho]		[Cr]		[NAA]		[mI]		Cho/Cr		NAA/Cr		mI/Cr		Cr/Cho		NAA/Cho		mI/Cho	
	Hippo-campus	Mean Con-centration (mmol/kg)		Mean Con-centration (mmol/kg)		Mean Con-centration (mmol/kg)		Mean Con-centration (mmol/kg)		Mean ratio		Mean ratio		Mean ratio		Mean ratio		Mean ratio		Mean ratio	
Normal Control (n=17)	Left	0.64± 0.10		6.11± 0.61		15.15± 2.26		0.07± 0.12		0.11± 0.02		2.51± 0.49		0.01± 0.02		9.73± 1.49		24.05± 4.09		0.11± 0.16	
	Right	1.28± 0.13		8.44± 1.10		11.68± 1.51		0.16± 0.22		0.15± 0.02		1.41± 0.28		0.02± 0.02		6.72± 0.93		9.29± 1.88		0.12± 0.16	
		Compared to normal control using two-samples t-test																			
HIV+ (n=13)	Left	0.72± 0.07	0.023 *,↑	6.84± 0.97	0.018 *,↑	15.17± 1.72	0.979	0.24± 0.19	0.005 **,↑	0.11± 0.02	0.732	2.26± 0.39	0.138	0.04± 0.03	0.004 **,↑	9.55± 1.50	0.751	21.15± 2.16	0.028 *,↓	0.34± 0.25	0.006 **,↑
	Right	1.34± 0.22	0.350	9.52± 1.48	0.029 *,↑	10.69± 0.96	0.049 *,↓	0.37± 0.39	0.074	0.14± 0.02	0.177	1.15± 0.22	0.010 *,↓	0.04± 0.04	0.067	7.23± 1.36	0.233	8.18± 1.48	0.092	0.29± 0.34	0.076
NS+ (n=12)	Left	0.76± 0.09	0.005 **,↑	7.19± 1.10	0.002 **,↑	14.71± 3.18	0.664	0.24± 0.17	0.003 **,↑	0.11± 0.02	0.771	2.09± 0.53	0.037 *,↓	0.03± 0.02	0.003 **,↑	9.64± 1.77	0.884	19.63± 4.33	0.009 **,↓	0.31± 0.20	0.005 **,↑
	Right	1.28± 0.21	0.947	9.30± 1.62	0.097	10.53± 0.96	0.029 *,↓	0.30± 0.20	0.085	0.14± 0.02	0.071	1.16± 0.20	0.013 *,↓	0.03± 0.02	0.074	7.34± 1.17	0.1244	8.37± 1.18	0.147	0.23± 0.14	0.048 *,↑
nonHIV, nonNS (n=7)	Left	0.73± 0.10	0.215	6.04± 1.73	0.525	14.71± 3.54	0.516	0.19± 0.16	0.358	0.13± 0.03	0.049 *,↑	2.49± 0.55	0.942	0.03± 0.02	0.167	8.23± 2.07	0.116	20.05± 4.51	0.094	0.26± 0.19	0.372
	Right	1.30± 0.15	0.612	9.34± 2.53	0.142	10.44± 2.20	0.307	0.40± 0.27	0.071	0.15± 0.05	0.644	1.14± 0.15	0.052	0.04± 0.02	0.071	7.20± 1.84	0.398	8.10± 1.86	0.171	0.30± 0.20	0.055

Key: Cho, choline; Cr, creatine; mI, myo-inositol; mmol/kg, millimole per kilogram per brain tissue; NAA, N-acetyl-aspartate; r, Pearson correlation coefficient; ↑, significant increase compared to control; ↓, significant decrease compared to control; *indicates $p<0.05$, **$p<0.01$.

NAA (p=0.049) and a trend to higher mI (p=0.074) compared to normal controls.

There were significant increases in mI/Cr (p=0.004) and mI/Cho (p=0.006), and decrease in NAA/Cho (p=0.028) in the left hippocampus. In the right hippocampus, there was a significant decrease of NAA/Cr (p=0.010) and a trend of significant increase in mI/Cr (p=0.067) while the other metabolite ratios in bilateral hippocampi showed no significant difference.

Mean absolute concentrations of metabolites and metabolite ratios in NS+ patients

In the left hippocampus, NS+ patients showed significantly higher Cho (p=0.005), Cr (p=0.002) and mI (p=0.003) compared to normal controls. In the right hippocampus, NS+ patients showed significantly lower NAA (p=0.029) compared to normal controls.

There were significant decrease in NAA/Cr (p=0.037) and NAA/Cho (p=0.009), and significant increase in mI/Cr (p=0.003) and mI/Cho (p=0.005) in the left hippocampus, as well as a significant decrease in NAA/Cr (p=0.013) and a significant increase in mI/Cho in the right hippocampus (p=0.048), while the other metabolite ratios in bilateral hippocampi showed no significant difference.

Mean absolute concentrations of metabolites and metabolite ratios in non-HIV, non-NS patients

In the bilateral hippocampi, non-HIV, non-NS patients showed no significant difference in absolute concentration or metabolite ratio compared to normal controls, except increased Cho/Cr (p=0.049) in the left hippocampus after adjustment for age.

Discussion

It was recognized that HIV infection is associated with an increased risk of NS, especially early NS [16], and clearance of NS is problematic in HIV infected patients with low CD4 counts and uncontrolled viral load [18]. However, the extent of brain damage associated with concomitant infections has been deficient in the literature. We were first to demonstrate in a cohort of syphilitic patients, mixed HIV infection and NS cause substantial metabolic changes in the bilateral hippocampi, despite a paucity of MRI abnormalities in the structural scans.

In a neuroimaging study of 35 NS patients with a majority being HIV+ (91%), Brightbill et al. [12] found that cortical atrophy, cerebral infarctions, non-specific white matter lesions and arteritis occur in 37%, 23%, 7% and 2% of the patients respectively. Another study [24] of 14 HIV- NS patients detected cortical atrophy, cerebral infarctions, non-specific white matter lesions and arteritis in 50%, 43%, 50% and 29% respectively. In our cohort of 25 syphilitic patients (28% being HIV+ NS, 24% being HIV+ only, 20% being NS only, and 28% without HIV and NS), cortical atrophy, cerebral infarctions, non-specific white matter lesions (Fazekas' score- 2 or 3) and arteritis were present in 32%, 4%, 12% and 0% respectively.

The MRI findings indicated that the HIV+ or NS+ patients in our cohort did not have advanced structural disease. However, complex metabolic abnormalities were already demonstrated in both HIV+ and NS+ patients. In addition, these patterns revealed striking similarities, which could possibly be due to partial overlapping of patients in the subgroups, and/or the promotion of syphilitic CNS involvement in HIV-related immunocompromise [6, 7, 13-17].

In our cognitively normal HIV+ group (only 3 on HAART due to low CD4 count), we found significant increases in absolute concentrations of Cho, and mI, and metabolite ratios of mI/Cr and mI/Cho, and decreased NAA/Cho in left hippocampus, as well as decreases in absolute concentration of NAA and NAA/Cr, and a trend of increase in mI/Cr in the right hippocampus. Therefore, our hippocampal results were similar to previous studies of asymptomatic HIV subjects in the subcortical white matter/thalami [28-30, 32, 35]. Increased mI (or mI/Cr) and Cho (or Cho/Cr) in HIV+ patients have been attributed to increased glial activity and were found to increase with advancing ADC stages [1], and reflected the presence of inflammatory changes [33].

Contrary to a previous study [38], we found no significant change in Cho/Cr in the hippocampi of HIV+ group. The lack of significance could have been caused by the concomitant increases in absolute concentrations of the 2 metabo-

lites [1]. Therefore, quantification based on relative ratios of metabolites using Cr as reference has its drawbacks and could be misleading [1, 44].

Our finding of increase in Cr was contradictory to a prior study [30], which detected a decrease in Cr. However, their neurologically asymptomatic HIV patients were either Category B or C according to CDC classification, and likely be associated with impairment of energy metabolism. Nevertheless, HIV-dementia patients had shown both an increase and a decrease in Cr concentrations [1, 40] and the controversial role of Cr has not been resolved.

NAA decrement was found in moderate to severe ADC stages [1, 34], as well as mild degree of lowered N-acetyl-aspartate/creatine (NAA/Cr), or N-acetyl-aspartate/choline (NAA/Cho) or both in the subcortical white matter of asymptomatic HIV+ patients [28-30]. These reductions might represent early neuronal damage without gross anatomical abnormalities. An autopsy study [25] had shown that the HIV load in AIDS was not distributed uniformly, but showed higher levels in the basal ganglia and hippocampus than mid-frontal cortical gray matter. Hence, it was not surprising to detect lower NAA in the right hippocampus of our HIV+ group. We postulated that metabolic changes in HIV patients might occur early in the hippocampi, not being described previously in the literature. Moreover, interaction between NS and HIV might also be a factor.

In the NS+ group, significantly increased absolute concentrations of Cho, Cr and mI, decreased NAA/Cr and NAA/Cho and increased mI/Cr and mI/Cho in left hippocampus, and significantly decreased NAA and NAA/Cr and increased mI/Cho in right hippocampus were found. There is an increased awareness of mesial temporal T2 signal abnormalities in NS [21-24], but the etiology is still uncertain. Elevated inflammatory biomarkers such as Cho and mI in our study supported the hypothesis postulating that the signal change was due to a combination of edema and gliosis [21, 23].

In the current study, the profound metabolic changes in HIV+ and NS+ groups were in marked contradistinction from the 'negative' metabolic results in the non-HIV, non-NS group (except elevated Cho/Cr with borderline significance). The non-HIV, non-NS group comprised of 7 late latent syphilitic patients with neurological symptoms or persistently elevated VDRL titer after treatment, thereby mimicking NS clinically.

From the clinical standpoint, it is necessary to exclude NS in syphilitic patients at greatest risk, and some authorities suggested performing lumbar puncture on all patients with HIV and syphilis [6]. ^{1}H-MRS might serve as a non-invasive test for triaging patients with reactive syphilitic serology and neurological symptoms and signs suspicious of NS to undergo lumbar puncture or not. ^{1}H-MRS is rendered useless in patients with HIV co-infection as the metabolic changes overlap with NS. In HIV- patients, our results showed that ^{1}H-MRS could potentially rule out NS in such a group of patients. Validation of our results by a larger scale study is warranted.

Furthermore, similar to its use in evaluation of HAART in HIV [40, 41], future studies are envisaged to explore the role of ^{1}H-MRS in monitoring response of NS to treatment, by evaluation of normalization of the inflammatory metabolite markers such as mI and Cho.

The major limitation of our study was a small cohort size. Also, the patients within HIV+ subgroup were in varying stages of syphilitic disease and some were under HAART treatment. Similarly, four of the patients in the NS+ subgroup were under treatment. The complex interactions between NS and HIV should be elucidated in a future large cohort study by comparing exclusive HIV and NS subgroups with mixed HIV/NS subgroup, preferably before drug treatment.

In conclusion, patients with mixed HIV infection and NS were found to have substantial metabolic changes in bilateral hippocampi, despite the paucity of MRI abnormalities in the structural scans. Striking similarities in the complex metabolic patterns in mixed HIV infection and NS were demonstrated in the current study, suggesting potential interactions between the two diseases. Finally, ^{1}H-MRS holds promise to identify NS in non-HIV patients with reactive syphilitic serology and neurological symptoms.

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