Cognitive function, depressive symptoms and syphilis in HIV-positive and HIV-negative individuals

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Running title: Cognitive function, depression and syphilis

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Abstract

Aims: We evaluated associations between history of syphilis infection and both cognitive function and depressive symptoms in people living with HIV (PLWH) and comparable HIV-negative controls.

Methods: Syphilis serological tests, cognitive function and depression were assessed in PLWH and controls participating in the POPPY study. Cognitive test scores were converted to demographically-adjusted T-scores (mean=50, SD=10) and then averaged to obtain a global T-score. Severity of depressive symptoms was assessed via the Patient Health Questionnaire (PHQ-9). Associations of syphilis with global T-scores and depression were assessed using median regression.

Results: The 623 PLWH and 246 HIV-negative controls were predominantly male (89.3% and 66.5%) with median age (interquartile range, IQR) of 57 (53-63) and 58 (53-63) years, respectively. PLWH had lower global cognitive T-scores [median (IQR) 48.7 (45.1, 52.1) vs. 50.5 (47.0, 53.9), p<0.001], more severe depressive symptoms [median (IQR) 4 (1, 10) vs. 1 (0, 3), p<0.001] and were more likely to report history of syphilis infection (22.0% vs. 8.1%) than controls. There was no significant association between history of syphilis and global cognitive function in either PLWH (p=0.69) or controls (p=0.10). Participant with a history of syphilis had more severe depressive

symptoms [median (IQR) 4 (1, 9) vs. 2 (0, 8), p=0.03], however, the association became non-significant (p=0.62) after adjusting for HIV-status and potential confounders.

Conclusions: Despite the higher prevalence of syphilis infection in PLWH, there was no evidence of an association between history of syphilis infection and impaired cognitive function nor depressive symptoms after accounting for potential confounders.

Introduction

In recent years syphilis has seen a resurgence with the incidence increasing after decades of decline (1). Untreated syphilis can cause serious neurological sequelae, including cognitive and psychiatric disorders (2), which may be more common in people living with HIV (PLWH) and may occur earlier in the course of the infection (3). Syphilis may be associated with cognitive impairment in PLWH (4), possibly as a result of higher rates of both symptomatic and asymptomatic neurological involvement in PLWH compared to HIV-negative controls. Indeed asymptomatic neurological involvement, based on cerebrospinal fluid findings, has been reported in 22.5% vs. 10% of PLWH and HIV-negative controls, respectively (5) as well as an increased use of single dose benzathine penicillin for the treatment of early syphilis, which may not be as effective as other therapies in clearing treponema from the central nervous system (6). However, the contribution, if any, of past syphilis to cognitive impairment and depressive symptoms reported in PLWH remains unclear as previous studies have not fully controlled for lifestyle factors that may confound any relationships with past syphilis, which may be a marker of risk-taking behaviour. Here, we sought to determine the relationships between past syphilis infection and both cognitive function and depressive symptoms in a cohort of PLWH representative of people attending for care in the UK, as well as in demographically comparable HIV-negative controls. Our hypothesis was that HIV-infection would modify the relationship between syphilis and cognitive function with past

infection of syphilis being associated with poorer cognitive function and more depressive symptoms in PLWH.

Methods

Study design and participants

The Pharmacokinetic and Clinical Observations in People Over Fifty (POPPY) study recruited a cohort of PLWH aged over 50 years as well as control cohorts of younger PLWH aged under 50 years and demographically comparable HIV-negative people aged over 50 years from HIV clinics, sexual health clinics and targeted community groups as described previously (7). Inclusion criteria for the groups of PLWH were: documented presence of HIV infection, self-defined white or black-African ethnicity, likely route of HIV acquisition via sexual exposure (either by male to male exposure if white or by heterosexual exposure if white or black-African) and the ability to comprehend the study patient information leaflet. The two control groups were frequency matched on gender, ethnicity, sexual orientation and location (in or out of London) to the group of older PLWH (with the control group of HIV-negative people additionally frequency matched for age). The study was approved by the UK National Research Ethics Service (NRES; Fulham London, UK number 12/LO/1409). All participants provided written informed

consent. The present analyses used information from the baseline POPPY visit only and included only the two older cohorts.

Definition of syphilis infection

Results of Treponema pallidum particle agglutination test (TPPA), rapid plasma regain (RPR) test and self-reported history of syphilis were combined to defined past and possible current syphilis infection as detailed in Table 1. Serology was undertaken locally at each POPPY clinical site with the screening algorithms dependent on local practice. Briefly, a history of syphilis infection was defined as either a positive Treponema pallidum particle agglutination test (TPPA) or a positive rapid plasma regain (RPR) test confirmed by a self-reported history of syphilis. A negative TPPA and/or RPR and a negative TPPA with a positive RPR but without a self-reported history of syphilis were considered as indicative of no history of syphilis infection.

Assessment of cognitive function and depressive symptoms

Assessment of cognitive function was performed using the CogState™ (Melbourne, Australia) battery (8), a computerised battery that has been previously used in cohorts of PLWH (9, 10). The assessment covered six cognitive domains, as described previously (11) and summarised in supplementary material. Quality checks were applied to ensure that scores were generated from completed and fully-understood tasks for each subject. Individual test scores were transformed as appropriate and converted into T-scores (mean

of 50 and standard deviation of 10) accounting for age, gender, ethnicity and level of education, using the HIV-negative control group as the reference population. A global T-score was calculated by averaging individual domain T-scores with higher values indicating better cognitive function.

Depressive symptoms were evaluated using the Patient Health Questionnaire-9 (PHQ-9), the recommended tool for the assessment of depression in PLWH (12), with scores ranging from 0 (no depression) to 27 (severe depression) (13).

Statistical analysis

Pairwise group comparisons of socio-demographic and self-reported lifestyle characteristics between older PLWH and similarly-aged HIV-negative controls and between those with a history of syphilis and those without, were assessed using Chi-square and Wilcoxon rank-sum tests as appropriate. The independent effects of syphilis and HIV-status (also independent of potential confounders) on both outcomes were evaluated using median regression models to minimise the influence of large outliers. Socio-demographic and lifestyle factors were included as potential confounders if they were significantly associated with the outcome (cognitive scores or depressive symptoms) and with a history of syphilis infection. Factors considered included age, gender, ethnicity, level of education, sexuality, self-reported smoking, alcohol consumption and recreational drug use in the past six months. We also evaluated interactions between

syphilis infection and HIV-status, to test whether the associations between syphilis and each outcome differed across PLWH and HIV-negative controls. All analyses were performed using SAS v9.4 with p-values <0.05 considered as statistically significant.

Results

Participant Characteristics

The 625 PLWH (median (IQR) CD4$^+$ T cell count of 613 (470, 792) cells/µL; 92.5% with HIV RNA <50 copies/mL) and 248 HIV-negative controls were comparable in terms of age and smoking status (Table 2). However, PLWH were more likely to be male, men who have sex with men (MSM) and to have reported recreational and injected drug use but less likely to be current consumers of alcohol compared to HIV-negative controls.

PLWH had overall poorer cognitive scores and more severe depressive symptoms compared to HIV-negative controls (median [IQR]: 48.7 [45.1, 52.1] vs. 50.5 [47.0, 53.9] and 4 [1, 10] vs. 1 [0, 3] p's<0.001, Table 2). A total of 137 (22.0%) PLWH and 20 (8.1%) HIV-negative controls had a history of syphilis infection, with a significantly higher prevalence among PLWH than HIV-negative individuals (p<0.001).

Cognitive function

The median [IQR] global T-score was 48.4 [44.9, 52.1] and 49.4 [45.7, 52.8] in those with a history of syphilis and those without respectively (p=0.09, Table 2). Of note, there

was no association with poorer performance in any of the six cognitive domains, including working memory (median [IQR]: 49.8 [45.0, 54.9] vs. 50.4 [45.6, 54.4], p=0.60), visual (49.7 [44.1, 53.4] vs. 49.6 [44.7, 54.4], p=0.42) and verbal learning (48.8 [42.7, 55.1] vs. 49.0 [42.5, 55.1], p=0.65). The difference in the global T-score remained non-significant after adjusting for HIV-status (p=0.23, Figure 1A) and for other confounders (age and years of alcohol consumption) (adjusted difference (95% CI) was -0.7 (-1.9, 0.4), p=0.22). Additionally, there was no suggestion that the association between cognitive scores and a history of syphilis infection was modified by HIV-status (interaction p=0.71).

Depressive symptoms

Participants with a history of syphilis reported a 2.0 (0.7, 3.3) points higher median PHQ-9 score than participants without (p=0.03, Table 2). After adjusting for HIV-status, the difference (95% CI) remained but was smaller: 1.0 (0.2, 1.8), p=0.02. However, after adjustment for potential confounders (alcohol consumption, smoking, recreational and injected drug use) the magnitude of the difference (95% CI) was further reduced and was no longer statistically significant: 0.1 (-1.0, 1.0), p=0.62. There was no difference in depressive symptoms within both groups (p=0.68 and p=0.27 in PLWH and HIV-negative controls, respectively, Figure 1B), and no interaction between history of syphilis infection, HIV-status and depressive symptoms (p=0.47).

Discussion

Despite the increased prevalence of syphilis infection in PLWH, we did not find an association between past or possible current infection and impaired cognitive function nor depressive symptoms after accounting for potential confounders. Moreover, we did not find that HIV-status modified the relationships between current history of syphilis and cognitive function or depressive symptoms.

These data are important as, to our knowledge, this is the largest study of syphilis and cognitive function in PLWH. A previous study from the CHARTER cohort compared cognitive function in 82 PLWH with previous syphilis and 52 who had never been infected with syphilis (4). Those with prior syphilis did not have higher rates of depressive symptoms. However, past syphilis was associated with a higher global deficit score and a higher rate of impairment in the learning domain. This contrasts with our findings, but it should be noted that the association with impairment in learning was attenuated after accounting for methamphetamine use and was no longer statistically significant. The large sample size in our study, comprehensive assessment and recruitment of demographically comparable HIV-negative controls allowed adjustment for potential confounders that may have exaggerated differences in cognitive function previously observed (4) between those who did and did not have a history of syphilis infection. Other unmeasured confounders (for example high-risk sexual behaviours) may exist between

PLWH and controls, however, it is unlikely that these would act in the opposite direction of the confounders we considered. It should be noted that the definition of syphilis we used was fairly conservative, in that participants who were RPR positive but reported no prior history of syphilis were not considered to have syphilis, given our study population. However only 1 HIV-positive participant was RPR positive without reporting prior history of syphilis and it is therefore unlikely that this resulted in a substantial bias. Moreover, whilst worse cognitive function and depressive symptoms could have been observed in participants with current syphilis compared to those with past syphilis or no history of syphilis, the small number of participants who may have had current syphilis infection (a maximum of 27 PLWH and 3 HIV-negative participants if possible current syphilis is assumed in those with either a positive RPR and TPPA or a positive RPR confirmed by a self-reported history of syphilis when TPPA was not done) did not permit full investigations of these associations. We do not have data on the full treatment histories of syphilis to confirm if these individuals truly had untreated early syphilis or prior treated syphilis with persistent non-treponemal titers (sero-fast RPR). Of note, a sensitivity analysis in which individuals with possible current syphilis were excluded, yielded results that were comparable to the main results presented here (data of the sensitivity analysis not shown).

In addition, whilst almost all PLWH considered were on successful antiretroviral therapy (99% on treatment, 93% with a HIV RNA <50 copies/ml) reflecting current epidemics in

UK and Ireland (14), those not optimally treated and hence potentially with worse cognitive function and higher rates of syphilis infection, may be less represented in our study. Similarly, our findings were obtained in individuals aged over 50 years, so results cannot be generalised to younger cohorts of PLWH. As described above, an important limitation is the lack of accurate syphilis staging and treatment history. However, even if individuals with neurological involvement from syphilis received syphilis therapy not considered optimal for neurosyphilis, we would expect this to have increased the effect size observed and increased the presence of any neurological sequalae. Whilst syphilis can contribute to several psychiatric disorders (15), we only focused on depressive symptoms as depression is the most common psychiatric disorder in PLWH (16). Furthermore, the cross-sectional nature of our analyses limits our ability to establish temporal associations – future longitudinal analyses of this cohort may provide further insight to impact of past syphilis infection on changes in cognitive function and new-onset depressive symptoms.

In summary, in this large cohort of PLWH and HIV-negative controls we did not find evidence that a history of syphilis was *independently* associated with impaired cognitive function or depressive symptoms.

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Tables

Table 1: Definition of history of syphilis based on TPPA, RPR and patient-reported history

Definition	Serology (TPPA)	Serology (RPR)	Patient-reported history of syphilis	N (%) of PLWH	N (%) of HIV-negative	Comments
History of syphilis	Positive	Negative	Yes	86 (13.8%)	11 (4.4%)	Standard serology for treated syphilis
	Positive	Not done*	Yes	24 (3.8%)	6 (2.4%)	Standard serology for treated syphilis
	Positive	Positive	Yes	16 (2.6%)	1 (0.4%)	Sero-Fast RPR or early syphilis
	Negative	Positive	Yes	0 (0.0%)	0 (0.0%)	Early syphilis and not evolved positive TPPA serology
	Not done*	Positive	Yes	11 (1.8%)	2 (0.8%)	Sero-Fast RPR or early syphilis
No history of syphilis	Negative	Negative	No	168 (26.9%)	99 (39.9%)	Standard serology for no history of syphilis
	Negative	Positive	No	0 (0.0%)	0 (0.0%)	False positive RPR
	Not done*	Positive	No	1 (0.2%)	0 (0.0%)	False positive RPR
	Negative	Not done*	No	315 (50.4%)	128 (51.6%)	Standard serology for no history of syphilis
	Not done*	Negative	No	4 (0.6%)	1 (0.4%)	Standard serology for no history of syphilis

Note: * Not done – syphilis serology based on local practice at each POPPY site and therefore both TPPA and RPR not always undertaken at some sites.

Table 2: Demographic, lifestyle and HIV-related characteristics by HIV- and syphilis-status at enrolment

n (%) or median (IQR)	HIV-status			Syphilis		
	PLWH (n=625)	HIV-negative (n=248)	p	Current/past syphilis (n=157)	No syphilis (n=716)	p
Gender			<0.001			<0.001
Male	558 (89.3%)	165 (66.5%)		151 (96.2%)	572 (79.9%)	
Female	67 (10.7%)	83 (33.5%)		6 (3.8%)	144 (20.1%)	
Age [years]	57 (53, 63)	58 (53, 63)	0.07	58 (54, 64)	57 (53, 62)	0.03
Ethnicity			0.02			0.14
Black-African	73 (11.7%)	16 (6.5%)		11 (7.0%)	78 (10.9%)	
White	552 (88.3%)	232 (93.5%)		146 (93.0%)	638 (89.1%)	
Sexual orientation			<0.001			<0.001
MSM/homosexual	503 (80.5%)	128 (51.6%)		146 (93.0%)	485 (67.7%)	
Heterosexual	122 (19.5%)	120 (48.4%)		11 (7.0%)	231 (32.3%)	
Alcohol consumption			0.01			0.12
Never consumed	46 (7.3%)	12 (4.8%)		5 (3.2%)	53 (7.4%)	
Previously consuming only	81 (13.0%)	17 (6.9%)		131 (83.4%)	586 (81.8%)	
Currently consuming	498 (79.7%)	219 (88.3%)		21 (13.4%)	77 (10.8%)	
If current/previous consumption						
Years drinking	38 (33, 45)	41 (35, 46)	0.02	40 (35, 48)	39 (34, 45)	0.02
units/week	8 (3, 20)	10 (3, 20)	0.42	7 (2, 21)	9 (3, 20)	0.42
Smoking status			0.06			0.15
Never smoked	251 (40.4%)	110 (44.5%)		57 (36.5%)	304 (42.6%)	

Ex-smoker	239 (38.4%)	102 (41.3%)		61 (39.1%)	280 (39.2%)	
Current smoker	132 (21.2%)	35 (14.2%)		38 (24.4%)	129 (18.1%)	
Ever injected drugs	58 (9.3%)	4 (1.6%)	<0.001	23 (14.7%)	39 (5.5%)	<0.001
Recreational drugs	163 (26.1%)	38 (15.3%)	<0.001	48 (30.6%)	153 (21.4%)	0.01
Duration of HIV [years]	15.9 (10.1, 22.5)	N/A		16.5 (11.7, 23.5)	15.8 (9.5, 22.3)	0.08
CD4$^+$ T cell count [cells/mm^3]	613 (470, 792)	N/A		601 (496, 712)	620 (463, 810)	0.49
Nadir CD4$^+$ count [cells/mm^3]	180 (86, 270)	N/A		189 (100, 261)	180 (84, 272)	0.55
On antiretroviral therapy	617 (98.7%)	N/A		136 (99.3%)	481 (98.6%)	0.52
HIV RNA <50 copies/ml	576 (92.5%)	N/A		128 (93.4%)	448 (92.2%)	0.62
Global cognitive T-score	48.7 (45.1, 52.1)	50.5 (47.0, 53.9)	<0.001	48.4 (44.9, 52.1)	49.4 (45.7, 52.8)	0.09
PHQ-9 score	4 (1, 10)	1 (0, 3)	<0.001	4 (1, 9)	2 (0, 8)	0.03

Note: comparisons of duration of HIV, CD4$^+$ T cell count, nadir CD4$^+$ count, proportion on antiretroviral therapy and with HIV RNA <50 copies/ml between those with and without current/past syphilis were performed in PLWH only (n with past or current syphilis = 137).

Figure caption

Figure 1: Global cognitive T-scores (A) and severity of depressive symptoms (B) in those with and without history of syphilis infection in both PLWH and HIV-negative controls

Supplementary material

Supplementary table 1: Description of the cognitive tests administered

Cognitive domain	Tests	Description of the score
Visual Learning	Continuous paired associate learning test	Total number of errors across the seven rounds
	Groton Maze Learning test – delayed recall	Total number of errors made after a delay
	One card learning task	Arcsine of the square root of the proportion of correct responses
Psychomotor function	Detection task	Mean of the $\log_{10}$ transformed reaction times for correct responses
Visual Attention	Identification task	Mean of the $\log_{10}$ transformed reaction times for correct responses
Executive Function	Groton Maze Learning test	Total number of errors made in five consecutive trials
	Set shifting task	Total number of errors across the five rounds
Verbal Learning	International Shopping list	Total number of correct responses made in three consecutive trials
	International Shopping list – delayed recall	Total number of correct responses made after a delay
Working Memory and Attention	One back task	Mean of the $\log_{10}$ transformed reaction times for correct responses
		Arcsine of the square root of the proportion of correct responses
	Two back task	Mean of the $\log_{10}$ transformed reaction times for correct responses
		Arcsine of the square root of the proportion of correct responses