Low levels of neurocognitive impairment detected in screening HIV infected men who have sex with men: The MSM Neurocog Study

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Abstract

Background

This study aimed to determine the prevalence of HIV neurocognitive impairment in HIV infected men who have sex with men aged 18-50 years, using a simple battery of screening tests in routine clinical appointments. Those with suspected abnormalities were referred on for further assessment. The cohort was also followed up over time to look at evolving changes.

Methods

HIV infected participants were recruited at three clinical sites in London during from routine clinical visits. They could be clinician or self-referred and did not need to be symptomatic. They completed questionnaires on anxiety, depression, and memory. They were then screened using the Brief Neurocognitive Screen (BNCS) and International HIV Dementia Scale (IHDS).

Results

Two hundred and five HIV infected subjects were recruited. Of these, 59 patients were excluded as having a mood disorder and 2 patients were excluded due to insufficient data, leaving 144 patients for analysis. One hundred and twenty four (86.1%) had a normal composite z score (within 1sd of mean) calculated for their scores on the three component tests of the BNCS. Twenty (13.9%) had an abnormal z score of which seven (35%) were symptomatic and thirteen (65%) asymptomatic. Current employment and previous educational level were significantly associated with BNCS scores. Of those referred onwards for diagnostic testing only one participant was found to have impairment likely related to HIV infection.

Discussion

We were able to easily screen for mood disorders and cognitive impairment in routine clinical practice. We identified a high level of depression and anxiety in our cohort. Using simple screening tests in clinic and an onward referral process for further testing we were not able to identify neurocognitive impairment in this cohort at levels consistent with published data.

Introduction

In the era of successful antiretroviral therapy (ART) for HIV infection, clinical attention has shifted from AIDS defining conditions and opportunistic infections to other chronic comorbidities. A particular field of concern for patients and clinicians alike is that of HIV related neurocognitive impairment (NCI), where the aetiopathogenesis and epidemiology remains unclear[1,2,3,4]. No simple screening test has been shown to be effective in unselected subjects attending routine clinical services and it is this we hoped to address in this study. The gold standard, following medical and functional assessments, remains a formal neuropsychometric (NP) assessment[5,6,7]. This can be time consuming and intensive for both patients and those providing the test. Controversies exist as to whether milder forms of memory and cognitive impairments detected on such tests have any true clinical or prognostic significance, and the natural history of such problems is unclear[8,9]. This makes it difficult to recommend clear screening programmes for monitoring HIV related neurocognitive impairment (NCI). As well as diagnostic uncertainties, studies also have the problem of multiple confounding risk factors such as recreational drug and excess alcohol use, and co infections such as hepatitis C infection.

The prevalence of NCI is reported to be substantial[10,11,12,13,14,15,16,17] in some HIV infected cohorts, and this is mostly asymptomatic. These data remains controversial, due to confounding, difficulties with case selection and biases (both regarding diagnosis and management), particularly in patients with full HIV suppression in plasma. There is a notable dearth of published data with good control groups for comparison to HIV infected cases.

Chelsea and Westminster Hospital (CWH) has a large HIV infected cohort of which a significant proportion are men who have sex with men (MSM). The cohort is ageing and concerns about memory problems exist for patients, concerns that are often shared by clinicians. We thus aimed to assess a validated, reliable and easily deliverable screening battery for routine clinical use at CWH. Much neurocognitive research has focussed on patients without hepatitis C coinfection or current recreational drug use, which can limit generalisability in clinical practice. We aimed here to investigate the utility of screening in a real world cohort, without exclusion of these groups.

Our objectives were thus to describe the prevalence of a positive screen for NCI using the Brief Neurocognitive Screen (BNCS), and to follow neurocognitive function over time. In order to be able to study a real clinical cohort, including those with hepatitis C infection and ongoing recreational drug use, we limited our

focus to MSM, in order to examine a group that comprise a substantial proportion of our clinics' HIV infected patients. Here we present baseline and follow-up data from this study.

Methods

The MSM Neurocog Study is a prospective cohort study investigating cognitive function in MSM aged 18-50 years. Subjects were either referred by their clinician or could self-refer when attending routine outpatient HIV clinics. They did not have to be symptomatic. We aimed to collect data on around two hundred persons living with HIV infection (PLWH). Data were collected regarding patient demographics, medical history, current and nadir CD4 count, current and peak viral load, ART use, and recreational drug, tobacco and alcohol use. Subjects were screened for depression (using the Patient Health Questionnaire, PHQ-9), anxiety (Generalised Anxiety Disorder questionnaire, GAD-7), and for subjective memory problems (Everyday Memory Questionnaire, EMQ). Neurocognitive testing was done using the International HIV Dementia Scale (IHDS)[18] and Brief Neurocognitive Screen (BNCS)[19]. Screening was done by research staff trained in administering the test, but in a regular clinic setting alongside routine HIV clinical services.

Subjects where included if they were 18-49 years inclusive, identifying as MSM, willing and able to provide written informed consent, able to complete screening tools and fluent in spoken and written English. Patients co-infected with chronic hepatitis B/C (diagnosed serologically at least 6 months prior to study to exclude seroconversion/recent infection) and/or currently using recreational substances including alcohol were also included, and HIV infected subjects had to have HIV of at least 6 months duration (in order to exclude symptoms associated with primary HIV infection).

Subjects were excluded if they had HIV or hepatitis B/C infection thought to have occurred in the preceding 6 months, current/active central nervous system (CNS) opportunistic infections or CNS malignancies, previous cerebrovascular accidents (CVA/stroke)/history of transient ischemic attacks (TIAs), or neuromuscular disease that would limit ability to perform the screening tests. Patients receiving current therapy with ribavirin or interferon for hepatitis co-infection or expected to start such therapy in the coming 12 months, or with a current medical or psychiatric/psychological condition deemed significant by the investigator were also excluded.

The PHQ-9, GAD-7, EMQ, IHDS have fixed numerical cut-offs which define 'caseness' and can be interpreted in real time. The BNCS comprises three short tests – TrailMaking A (TMA), TrailMaking B (TMB) and Digit Symbol testing (DST). BNCS and IHDS by themselves are insufficient to formally diagnose HIV related NCI and subjects with suspected impairment were referred to our Department of Psychological Medicine for further assessment and formal neuropsychological testing. 'Suspected impairment' was defined as the patient being symptomatic, scoring less than 10 on the IHDS, or having an abnormal score on at least one component test of the BNCS (TMA > 60 seconds, TMB > 90 seconds, DST <30 correct symbols).

For statistical analysis we calculated a composite neuropsychological (NP) z score for each subject based on the distance of their score from the mean in each of the three component tests. We used participants in the study to construct a normal range after exclusion of anxiety and depression, then compared individual scores to this range. This approach ran the risk of undercalling NCI but was certain to detect more severe cases (i.e. more likely to be specific than sensitive). We repeated the analyses including those with high anxiety and depressions scores. We also compared test scores to published data and found no difference in terms of those identified as being impaired. All PLWH identified as having suspected impairment were seen to fall into the group with abnormal BNCS scores determined statistically.

Milder forms of NCI than HIV associated dementia (HAD) are described as 'asymptomatic neurocognitive impairment' (ANI) or 'mild neurocognitive disorder' (MND)[20]. Both these conditions are defined as being at least one standard deviation from the mean on testing of two out of five neuropsychological domains, and the difference between the two is the presence or absence of symptoms. Symptoms in this case were defined as answering 'yes' to either or both of the following questions:

- Have you noticed any reduction in your mental functioning or ability to deal with things at work, at home or with other people?
- Have others commented on a mild decline or worsening in your mental functioning or ability to deal with things at work, at home or with other people?

Statistics

Chi-squared and Fishers exact tests were used to assess if differences existed with regards to categorical variables amongst those who had a normal composite z-score and those who did not. Mann-Whitney tests were used for continuous variables.

Results

Two hundred and five HIV infected subjects were screened. In our clinical practice we would address depression and anxiety related problems before proceeding to a formal neuropsychological assessment. Fifty-nine (28.8%) were excluded from this cohort as having a mood disorder, with GAD-7>10, PHQ-9>15 or both, and a further 2 patients were excluded as no data on GAD-7 or PHQ-9 was recorded. This left one hundred and forty four HIV+ for analysis. One hundred and twenty four (86.1%) had a normal z score (within 1sd of mean). Twenty (13.9%) had an abnormal z score of whom seven (35%) were symptomatic and thirteen (65%) asymptomatic (initial analysis below performed on these twenty subjects as one group).

Objective tests

Those with an abnormal BNCS score were less likely to be educated at University level/beyond (40.0% vs. 62.1%, p=0.02) or in skilled work (45.0% vs. 81.5%, p <0.0001) (Table 1). Current/ex recreational drug use was similar in both groups (80.0% in BNCS abnormal vs. 78.7%) with no significant association to score. Eighteen patients with abnormal z were receiving ART and individual agents were not associated with abnormality. There was no demonstrable CD4 association with an abnormal z score (median CD4 nadir 244 in both normal and abnormal z scoring groups, p=0.38). Of note, median age was statistically different and those with abnormal z were more likely to be older (normal 41y vs. abnormal 44y p<0.0001). BNCS outcome is known to be age related and a reanalysis was undertaken using three age tertiles. This showed normal z scores to be evenly spread between age groups but 50% of those with an abnormal z were in the group above 44y (p= 0.24). IHDS correlated with an abnormal BNCS (60% of BNCS abnormals had abnormal IHDS vs. 15.3% of normal, p<0.0001). Of the 20 impaired at screening five were offered repeat screening and a further six were offered neuropsychometric testing (three attended). Of the three, only one has shown

impairment to date that has been attributed as possibly due to HIV infection itself. This patient had significant co-morbidities noted, highlighting the complexities of assessment in this patient group, and it was thus not possible to solely attribute impairment to HIV.

It was noted that 20 participants overall were not receiving ART (eighteen normal z, two abnormal z). Reanalysis without including these twenty individuals showed similar results and individual ART agents remained unassociated with an abnormal z score. 151 participants had an undetectable viral load (<40 copies/ml) at the time of screening, 3 had no data recorded and 49 had a detectable viral load (median 5892; IQR 258-55994). Those not on ART had the higher recorded viral load results and all had normal z scores.

We also undertook an analysis comparing only the seven subjects with an abnormal z score and reported symptoms compared to those with normal z score. 5/7 (71.4%) were unemployed as compared to 14/124 (11.3%) of those scoring normally (p=0.0002). This group was also significantly more likely to have an abnormal EMQ score and an abnormal IHDS (4/7; 57.1% compared to 19/124; 15.3% (p=0.005)).

Subjective data

Subjects with an abnormal BNCS score self-scored significantly worse overall on the EMQ-total (25% vs. 2.4% of those with normal BNCS; p=0.001) (Table 2). Despite this, 75% of those with abnormal BNCS had a normal EMQ score, suggesting that EMQ may not be the best screener for potential NCI.

In terms of asking questions regarding function, the proportion of those who self-identified problems was the same whether z score was normal or abnormal. Forty (32.3%) of those with a normal z identified themselves as not having any problems affecting their ability to cope with things normally at work, home or school, whilst seven (35%) of those with an abnormal z score identified as having problems (p=0.80). For 'symptoms reported by others' 12.9% or those with normal z being identified as having problems compared to 30% of those with an abnormal z (p=0.09).

Inclusion of those with high anxiety/depression scores

Comparing our analyses to the total dataset, age became no different between the impaired and unimpaired groups [Table 1]. Marital status becomes important, with those who were married or in a civil partnership being much more likely to be unimpaired (p=0.003) [Table 1]. You were much more likely to report symptoms yourself, or have them reported by others, if you scored highly for anxiety or depression [Table 2].

Follow up data

Follow up screening was done at any single time point 6-12 months after the initial visit, in order to coincide with a regular HIV follow up appointment. Full follow up data are available in twenty-seven subjects. Other subjects were not picked up at follow up visits, did not attend within window or declined further screening.

In these subjects the average scores of the subjective data, and the IHDS, were compared and none of these (GAD7, EMQ, IHDS) were any worse at follow up (data not shown). Depression scores did show a general tendency to improve (53.5% at baseline scoring $\geq$10 compared to 33.3% at follow up, p=0.06).

Although there were a limited number of subjects with full baseline and follow up data, a comparison of individual baseline scores with those at follow up was performed. In terms of depression screening, those with high or low scores did not show any differences. Of those with PHQ <10 at baseline, 10/18 (83.3%) remained <10 at follow up. For those scoring $\geq$15, 5/8 (55.6%) remained in this group at follow up. Anxiety followed a similar pattern. For EMQ scores, most of those with normal scores remained normal at follow up, but those with abnormal scores seemed to have a good chance of normalising their score at follow up (Table 3). This might represent genuine improvements, a learning effect, or lower anxiety/depression, possibly regarding their health or cognition.

In terms of BNCS testing there was improvement in average values for all three component tests at follow up as compared to baseline, and this was significant (Table 4). It is difficult to comment on how much learning effects may have accounted for these changes.

Using published scores rather than comparing to our own test population

We reassessed our analysis using the published normative data for the three composite BNCS tests[21]. Contrary to expectations this yielded the same results. Twenty participants had an abnormal score (composite z score >1sd from the published means), and these turned out to be the same subjects as those identified for our initial method. Given concerns about the lack of good controls for HIV in this area this is clearly of interest and worthy of further exploration in a larger study.

Discussion

Among 144 MSM living with HIV infection, without anxiety or depression, the overall prevalence of a positive screen for NCI was 20/144 (14%). Of these only 13/144 (9%) were symptomatic. This is extremely low compared to other historical published data although comparable to data recently published from the UK that found minimal cognitive impairment in UK HIV infected MSM[13,15,22]. It is worth bearing in mind that other studies may have different entry criteria, including different age cut offs.

Whilst we excluded those with significant anxiety and/or depression scores, it is worth remembering that anxiety and depression may also be presenting features of underlying NCI. We do show data comparing our test set to our entire dataset at baseline and not many significant differences are shows.

We identified only one possible case of HIV related NCI, which is not to suggest that it does not exist, rather that, perhaps, for a significant proportion of our patients, it is not a clinically relevant problem, although we did only managed to contact and rescreen a low proportion of subjects at 6-12 months.

A separate analysis comparing scores in our group with high anxiety and depression scores showed worse performance in this group regarding neurocognitive tests. We have not included this group in our analysis for clarity, but an important question is whether reversing the depression or anxiety improves neurocognitive functioning, or if there is underlying NCI that is worse in this group. This issue is not answered in this study.

In terms of simplifying screening, we looked at how the IHDS and EMQ questionnaires faired in terms of detecting those with a subsequent abnormal BNCS score, as well as the reporting of symptoms by others. In this regard, IHDS has sensitivity of 0.60 and specificity of 0.85. This pattern is born out for EMQ and ‘symptoms reported by others’. Scoring normally on these criteria is reassuring in terms of not having an abnormal BNCS score, but being positive is not a good predictor of impairment. In this case this could work

well for routine clinic appointments as physicians can reassure those who are likely to be normal, whilst referring on for further investigating those who do not do so well on these simple tests.

We did not show an association with nadir CD4 count that has been suggested as a previous risk factor for NCI. Furthermore we only identified one case of possible HIV related cognitive impairment. This may underestimate the true prevalence but does show the difficulties clinicians face in implementing scoring programmes or detecting those requiring further assessment. It is worth consideration that only 3/20 impaired on screening tests underwent full assessment and outcomes for the other 17 are not known.

There are limitations. The BNCS and IHDS have previously been reported to be limited in their ability to detect milder cognitive impairment[23,24], but were selected here to allow easy, clinic based screening. Constructing our own reference range is novel, and better data from an HIV negative population for comparison would be useful. There is an inherent circularity in using the HIV infected group as its own reference, but initial comparison of results using this method to one using published normative data for the BNCS suggests that our method was equivalent. Further assessment of these two methods of analysis is warranted on a larger sample size to determine statistical validity. Whilst the study had unselected recruitment this does not avoid a possible bias towards enrolment of those with symptoms. The low level of those attending for follow up is also a limitation for any conclusions about progression. With a fairly short time period between baseline and follow up there could be a learning effect, especially in this cohort with a high educational level.

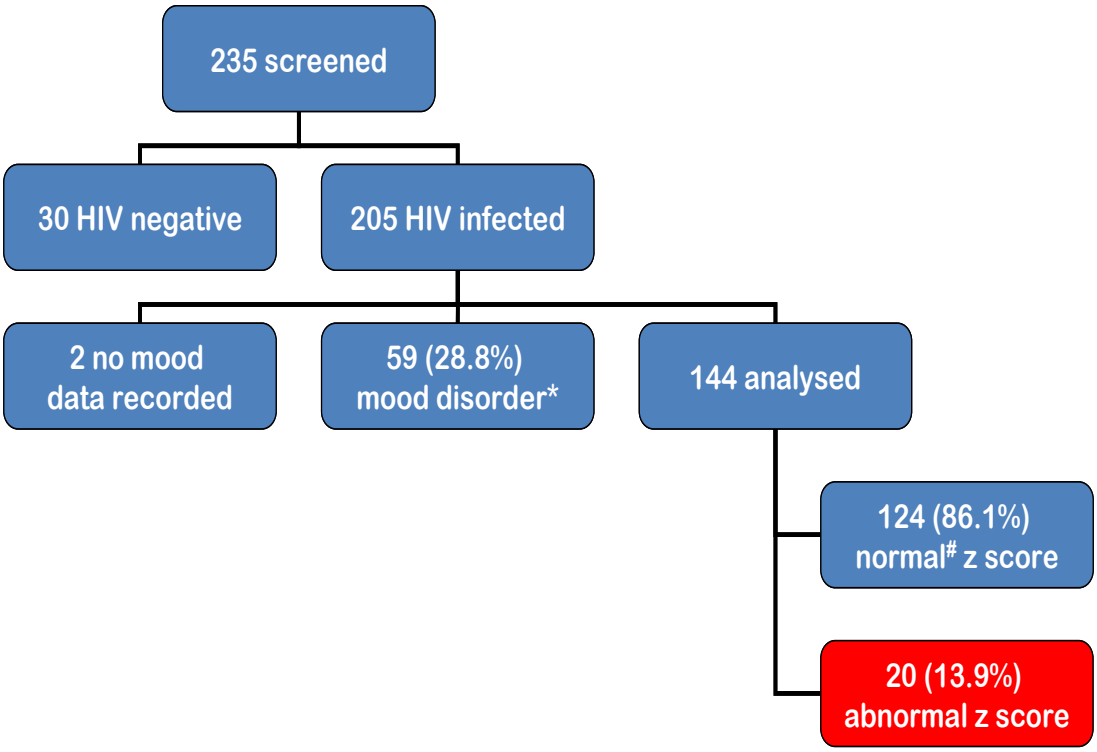
The larger, Abbvie-funded CRANium Study[25] was published after commencement of the MSM Neurocog Study. There are some notable differences in that the CRANium Study, whilst also using BNCS, excluded recent drug or excessive alcohol use, used the Hospital Anxiety and Depressions Scale (HADS) and set out to compare those not receiving ART with those receiving either non nucleoside, or protease based, antiretroviral therapy. They also pre-established that 40% of participants should be female. More than 40% of participants did have a positive screen for NCI, and a significant number demonstrated a mood disorder on screening. The most important difference to our study is that no attempt was made to show that these screen positive participants, following only the three composite tests of the BNCS, had a true underlying deficit as demonstrated by formal neuropsychometric testing.

We show high anxiety, depression and current/previous recreational drug use in HIV infected MSM aged 18-50 years. Patient pathways should include screening for anxiety, depression and substance use, but in this

young MSM group a positive screen from a basic, clinic based combination of screening tools did not seem to identify high numbers with true neurocognitive impairment. Caution should be made when recommending simple screening tests in the general clinic setting without further evaluation.

Charts and Tables

Flowchart 1



**of which 7 symptomatic and 13 asymptomatic*

#within 1sd of mean

**GAD7>10, PHQ9>15* or *both*

Table 1: Data from baseline visit

		HIV +, normal composite Z-score (exc anxiety/depression)	HIV +, composite Z-score > 1 SD below mean (exc anxiety/depression)	P-value	HIV +, normal composite Z-score (inc anx/depression	HIV +, composite Z-score > 1 SD below mean (inc anx/depression	P-value
N		124	20		170	35	
Age (yrs)	Median (IQR)	41 (37, 45)	44 (40, 49)	<0.0001	42 (37, 46)	44 (38, 48)	0.09
Nationality n (%)	White	107 (86.3)	18 (90.0)	0.99	149 (87.7)	28 (80.0)	0.45
Mother tongue n (%)	English	90 (72.6)	16 (80.0)	0.18	121 (71.2)	24 (68.6)	0.09
Marital status n (%)	Married/civil partnership	26 (21.0)	2 (10.0)	0.36	34 (20.1)	0 (0.0)	0.003
	Single	43 (34.7)	10 (50.0)		65 (38.5)	22 (64.7)	
	Partner	55 (44.4)	8 (40.0)		70 (41.4)	12 (35.3)	
Location n (%)	City	101 (82.1)	13 (65.0)	0.17	144 (85.2)	29 (85.3)	0.70
	Small town	5 (4.1)	1 (5.0)		6 (3.6)	1 (2.9)	
	Large town	13 (10.6)	5 (25.0)		14 (8.3)	4 (11.8)	
	Other	4 (3.3)	1 (5.0)		5 (3.0)	0 (0.0)	
Highest level of	Post-graduate	28 (22.6)	1 (5.0)	0.02	34 (20.1)	1 (2.9)	0.002
education n (%)	University	49 (39.5)	7 (35.0)		69 (40.8)	9 (26.5)	
	College	24 (19.4)	2 (10.0)		34 (20.1)	9 (26.5)	
	School	23 (18.6)	10 (50.0)		32 (18.9)	15 (44.1)	
Occupation n (%)	Skilled employed	101 (81.5)	9 (45.0)	<0.0001	130 (76.5)	11 (32.4)	<0.0001
	Unskilled employed	3 (2.4)	0 (0.0)		6 (3.5)	0 (0.0)	
	Unemployed	14 (11.3)	11 (55.0)		28 (16.5)	21 (61.8)	
	Student	6 (4.8)	0 (0.0)		6 (3.5)	2 (5.9)	
CD4 (cells/mm^3)	Median (IQR)	583 (426, 780)	601 (412, 738)	0.85	579 (426, 759)	564 (408, 748)	0.77
Nadir CD4 (cells/mm^3)	Median (IQR)	244 (137, 410)	244 (163, 292)	0.38	236 (120, 374)	206 (47, 339)	0.26
Illegal drugs taken	Current	42 (34.4)	5 (25.0)	0.64	58 (34.5)	12 (35.3)	0.99
	In the past	54 (44.3)	11 (55.0)		74 (44.1)	15 (44.1)	
	Never	26 (21.3)	4 (20.0)		36 (21.4)	7 (20.6)	
	Current cannabis	*12 (9.7)*	*2 (10.0)*	*0.99*	*21 (12.4)*	*3 (8.6)*	*0.53*
	Current cocaine	*24 (19.4)*	*2 (10.0)*	*0.53*	*36 (21.2)*	*4 (11.4)*	*0.19*
	Current methamphetamine	*11 (8.9)*	*0 (0.0)*	*0.36*	*14 (8.2)*	*1 (2.9)*	*0.27*
	Ex cannabis	*34 (27.4)*	*8 (40.0)*	*0.29*	*43 (25.3)*	*13 (37.1)*	*0.15*
	Ex cocaine	*44 (35.5)*	*9 (45.0)*	*0.46*	*62 (36.5)*	*14 (40.0)*	*0.69*
	Ex methamphetamine	*17 (13.7)*	*0 (0.0)*	*0.13*	*21 (12.4)*	*1 (2.9)*	*0.10*

Table 2: Other scores compared to composite z score

		HIV +, normal composite Z-score (exc anxiety/depression)	HIV +, composite Z-score > 1 SD below mean (exc anxiety/depression)	P-value	HIV +, normal composite Z-score (inc anx/depression	HIV +, composite Z-score > 1 SD below mean (inc anx/depression	P-value
N		124	20		170	33[1]	
EMQ: Impaired total	≤2.07	121 (97.6)	15 (75.0)	0.001	155 (91.2)	21 (63.6)	<0.0001
memory n (%)	>2.07 (impaired total)	3 (2.4)	5 (25.0)		15 (8.8)	12 (36.4)	
EMQ: Impaired retrieval	≤2.68	121 (97.6)	15 (75.0)	0.001	158 (92.9)	21 (63.6)	<0.0001
memory n (%)	>2.68 (impaired retrieval)	3 (2.4)	5 (25.0)		12 (7.1)	12 (36.4)	
EMQ: Impaired accrual	≤1.89	119 (96.0)	16 (80.0)	0.02	152 (89.4)	21 (63.6)	0.0001
memory n (%)	>1.89 (impaired accrual)	5 (4.0)	4 (20.0)		18 (10.6)	12 (36.4)	
IHDS score n (%)	≤10 (abnormal)	19 (15.3)	12 (60.0)	<0.0001	37 (21.9)	20 (60.6)	<0.0001
	>10	105 (84.7)	8 (40.0)		132 (78.1)	13 (39.4)	
Symptoms (self) n (%)		40 (32.3)	7 (35.0)	0.80	68 (40.0)	21 (60.0)	0.03
Symptoms (others) n (%)		16 (12.9)	6 (30.0)	0.09	36 (21.2)	13 (37.1)	0.04

Table 3: EMQ baseline and follow-up comparison (row %)

AVERAGE QUESTION SCORE	Impaired total memory follow up	
Impaired total memory baseline	≤2.07	>2.07
≤2.07	19 (90.5)	2 (9.5)
>2.07	3 (50.0)	3 (50.0)
	Impaired retrieval memory follow up	
Impaired retrieval memory baseline	≤2.68	>2.68
≤2.68	21 (95.5)	1 (4.5)
>2.68	3 (60.0)	2 (40.0)
	Impaired accrual memory follow up	
Impaired accrual memory baseline	≤1.89	>1.89
≤1.89	20 (95.2)	1 (4.8)
>1.89	3 (50.0)	3 (50.0)

Table 4: Baseline and follow-up comparisons in Trailmaking A (TMA), Trailmaking B (TMB) and Digit Symbol Testing (DST)

	Baseline Mean (SD)	Follow-up Mean (SD)	P-value[1]
TMA (low score good)	33.1 (12.4)	24.8 (7.8)	0.01
Age <35 (n=4)	*38.0 (14.9)*	*22.2 (5.4)*	
35-44 (n=13)	*32.2 (11.2)*	*27.8 (9.6)*	
>44 (n=11)	*32.4 (13.8)*	*22.4 (4.9)*	
TMB (low score good)	81.2 (29.8)	60.1 (28.6)	0.003
<35 (n=4)	*83.0 (16.0)*	*73.8 (38.8)*	
35-44 (n=13)	*78.0 (28.4)*	*50.8 (29.8)*	
>44 (n=11)	*84.4 (36.4)*	*66.2 (21.3)*	
DST (high score good)	49.1 (11.5)	58.5 (14.9)	0.003
<35 (n=4)	*47.8 (14.4)*	*63.5 (15.2)*	
35-44 (n=13)	*51.2 (11.4)*	*57.5 (14.9)*	
>44 (n=11)	*47.1 (11.3)*	*57.9 (15.9)*	
Composite Z-score	0 (0.84)	0 (0.73)	0.92

[1]Comparing baseline to follow up using Paired T-test

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