

BHIVA Best Practice Management Session

CNS (The brain) - **I keep forgetting things**

DEMENTIA DIAGNOSIS, CLASSIFICATION AND
INVESTIGATIONS

Paul Holmes

Consultant Neurologist

Guy's and St Thomas' Hospitals

Nothing to Declare

Patients presenting to your follow up HIV clinic with the complaint being one of forgetfulness

- With a longer life expectancy than before, people living with HIV are at an increased risk of developing non-AIDS comorbidities, such as cardiovascular diseases, cognitive disorders and cancers.
- Three likely cognitive presentations in clinic
 1. Memory complaint that links to HIV associated cognitive decline (HAND)
 2. Memory complaint related to anxiety and mood
 3. Memory complaint that links to a separate diagnosis such as Alzheimer's disease or vascular cognitive impairment

Approach to a patient with cognitive issues

- J.P. is a 62-year-old gentleman accompanied by his male partner who feels that he has **progressive** memory loss. J.P. denies any problems. Previously an accountant, he is **now unable to use his on-line bank account**. He has had difficulty with getting **lost** while driving to the gym. He has HIV infection since 2000 well controlled on ART.
- He was diagnosed with **depression** two years ago after his late partner died. He has **raised blood pressure**. His **father was diagnosed with Alzheimer's disease** at the age of 75.
- On examination, his BP is 172/91; he is oriented, scores 26/30 on the MMSE (0/3 recall and difficulty with the intersecting pentagon); he is unable to do the clockface.
- A few months later, his MMSE is 24/30; and he has some **mild cogwheel rigidity** and a slight shuffling gate, but no tremor. His partner reports that he has been having vivid visual **hallucinations and paranoid thought**.

Questions that might be in your mind

- What are the risk factors for dementia in his case and could HIV be implicated?
- What are some limitations to the MMSE. Has it been helpful in diagnosing the problem?
- Is there any association between his blood pressure and his cognitive issues?
- What is the definition of a dementia? What is the “line” between “normal” memory loss with age and dementia.
- What type of dementia might J.P. have?
- What investigations would be helpful?

Could J.P.'s cognitive impairment be linked to his HIV infection?

- Over the past three decades, the clinical presentation of HIV infection of the Central Nervous System (CNS) has evolved significantly
- The use of ART has significantly decreased the prevalence of severe forms of HIV-1 associated neurocognitive disorders (HAND)
- Neurocognitive dysfunction is however still reported with a very variable prevalence, ranging from 21% to 77.6%
- This very wide prevalence variance results largely from tests used to assess cognitive decline

What is the pathobiology of HAND?

- HIV-associated **chronic inflammation and associated neurotoxicity of long term ART**, as well as the **aging** of the HIV-infected population are most likely to influence the pathogenesis of HAND
- Changing treatment patterns with the **very early use of ART** will most likely alter the prevalence of HAND by preventing the inflammatory process in the brain as a sanctuary site
- Population with cognitive concerns are the **older population started on ART later** and in whom other co-morbidities may play a role
- **HIV enters the brain early in the course of infection** and can be detected in brain macrophages, microglia and astrocytes in presymptomatic individuals, suggesting that these cell types are important reservoirs for the virus

1

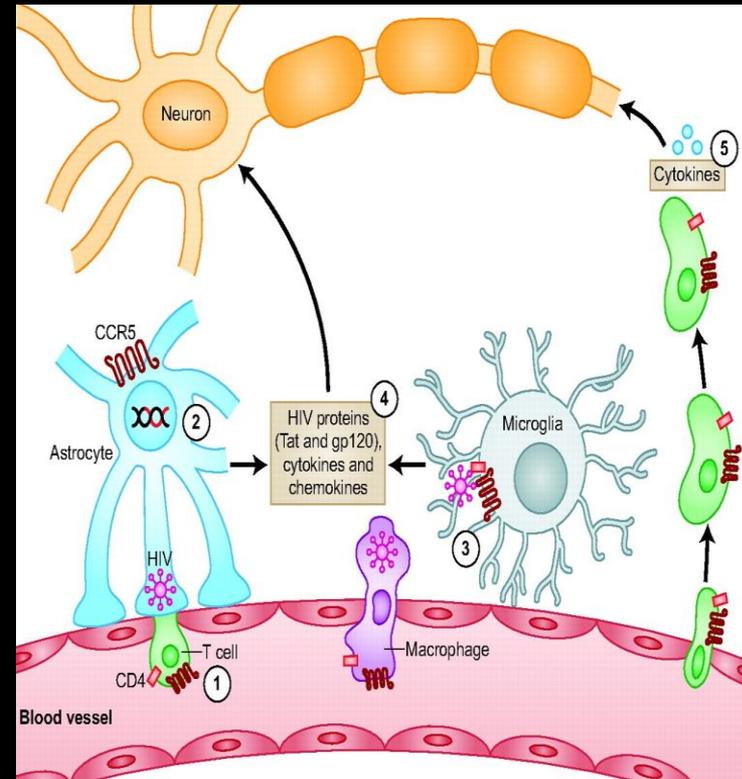
HIV can infect astrocytes by direct cell-cell contact with infected T cells through the virological synapse

2

After infecting astrocytes, HIV integrates into the genome where it remains latent

3

HIV-infected macrophages enter the brain early after initial infection. Next, HIV infection spreads to perivascular macrophages and microglia, a process that occurs when HIV enters the cell after binding to the CD4-receptor–CCR5 co-receptor complex.

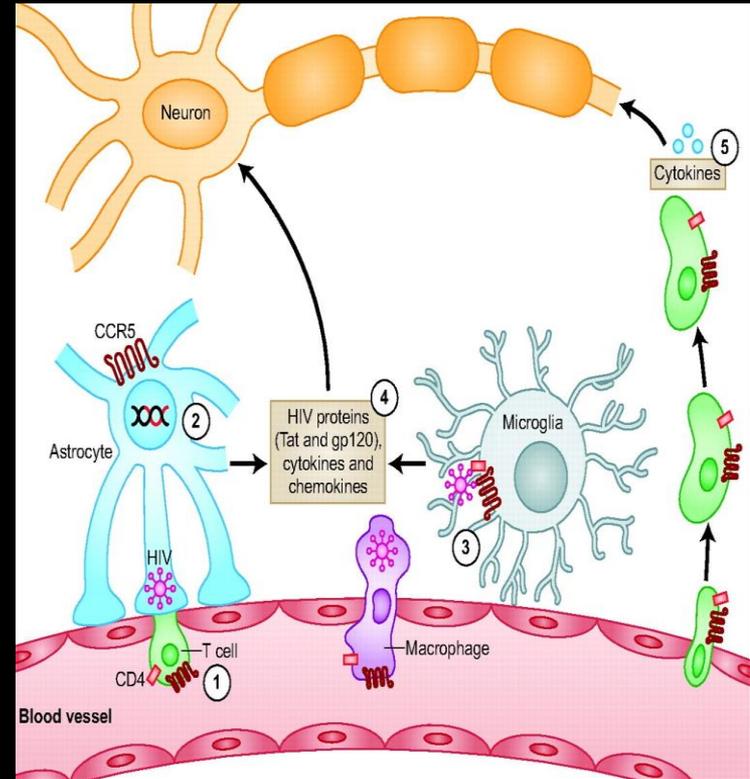


4

HIV-infected astrocytes and microglia cause neuronal injury indirectly by releasing soluble toxic viral proteins (Tat and gp120) and pro-inflammatory molecules (cytokines and chemokines)

5

Ongoing low levels of HIV replication in the CNS despite the use of cART promotes the entry of chronically activated T cells, which cause neuronal injury indirectly by releasing pro-inflammatory cytokines



Clinical features of HAND

- HAND is most consistent with that of other ‘subcortical’ disorders (e.g., Huntington’s disease), with deficits especially in the areas of motor skills, processing speed, and executive functions
- Severity of attention/working memory impairment among individuals with HAND appears to be driven by HIV disease severity as well as complexity or “load” of the attention/working memory task
- HIV-associated motor slowing is often seen in gait velocity, finger tapping and manual dexterity

What about tests?

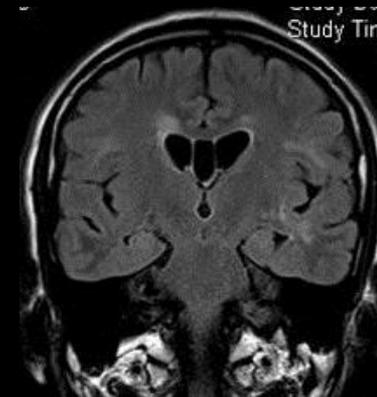
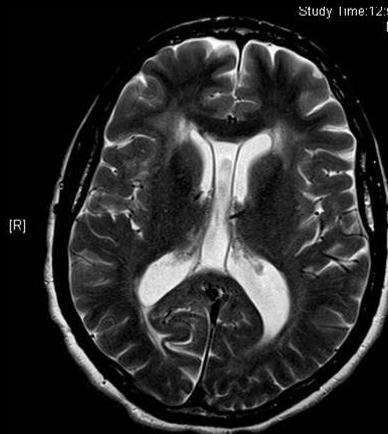
- MRI
- EEG
- CSF
- Neuropsychology
- CT/PET
- Other imaging

HIV-associated Neurocognitive Decline (HAND)

In the early stages of the AIDS epidemic, the most severe form of HAND was HIV-associated dementia (HAD) and typically occurred in patients with low CD4 counts. The onset was insidious and is similar to a vascular subcortical dementia with mental slowness, forgetfulness, poor concentration, changed behaviour with depression and mood swings and apathy.



Reproduced with permission from AIDS Images Library



This is the case of a MSM variably complaint on ART presents with headache and focal neurology including cognitive slowing. His CSF investigations showed.

Normal opening pressure of 16 cm/CSF
WCC 168 (95% lymphocytes, 5% polymorphs)

Glucose 3.6 mmol/l (serum glucose 5.1)

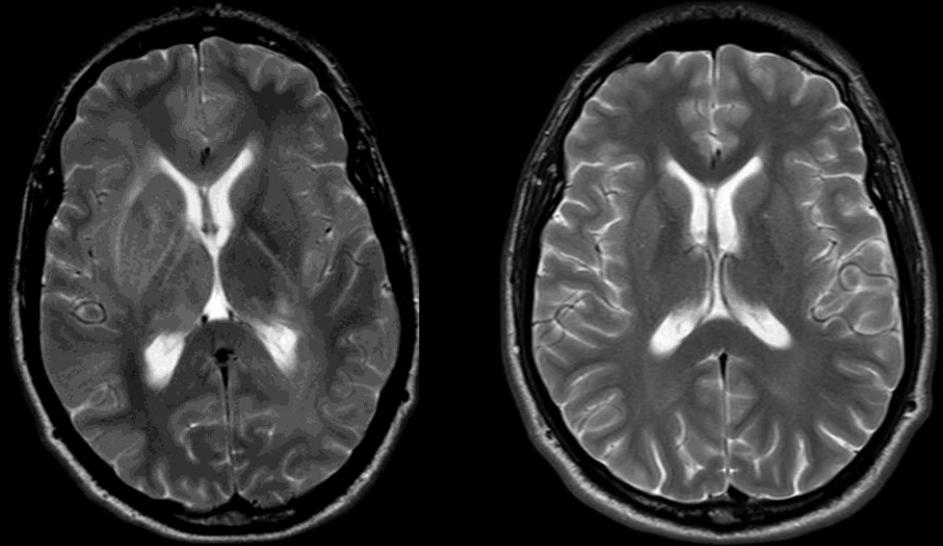
Protein 5.5 g/l protein

CSF HIV RNA 2128158 copies/ml

Serum HIV RNA 7358 copies/ml

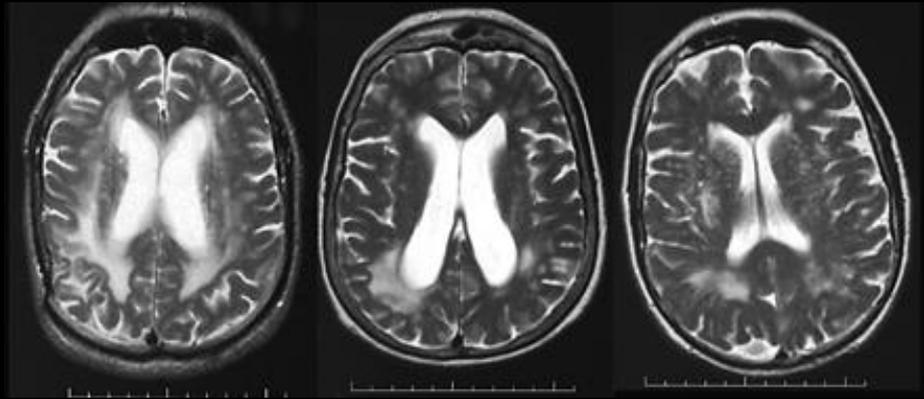
Other viral PCR studies negative

Unmatched OCB's in CSF



His MRI at presentation and then after compliance with ART is below. The MRI on the left shows significant swelling and white and grey matter signal change and this is an IRIS-type HIV encephalopathy with an inflammatory response to HIV in the CNS as described above and was treated with steroids and after compliance on ART the scan on the right shows resolution of the signal change. This is similar to a CD8 encephalitis.

Vascular risk and vascular cognitive impairment



Mounting data suggests that HIV infection leads to an excess risk of developing cardiovascular disease

HIV infection and treatment are more directly linked to atherogenesis, endothelial dysfunction, and coagulation abnormalities, likely through inflammation and immune dysregulation

Same risk reduction strategies that are used in HIV-uninfected individuals should apply (statin therapy, blood pressure control, and management of diabetes, smoking cessation)

What about Alzheimer's Disease in J.Ps presentation?

Diagnostic criteria for Dementia of the Alzheimer's Type

A. The development of multiple cognitive deficits manifested by both (1) memory impairment (impaired ability to learn new information or to recall previously learned information) (2) one (or more) of the following cognitive disturbances:

(a) aphasia (language disturbance)

(b) apraxia (impaired ability to carry out motor activities despite intact motor function)

(c) agnosia (failure to recognize or identify objects despite intact sensory function)

(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterised by gradual onset and continuing cognitive decline.

Diagnostic criteria for Dementia of the Alzheimer's Type

The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

1. Other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, **Parkinson's disease**, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumour)

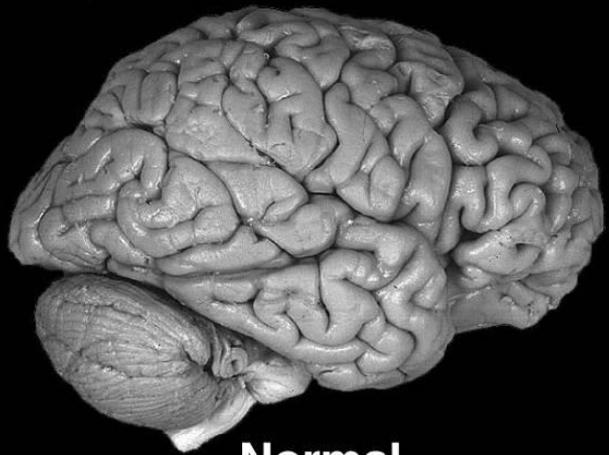
2. Systemic conditions that are known to cause dementia (e.g., vitamin B or folic acid deficiency, hypothyroidism, niacin deficiency, hypercalcemia, neurosyphilis, **HIV infection**)

3. Substance-induced conditions

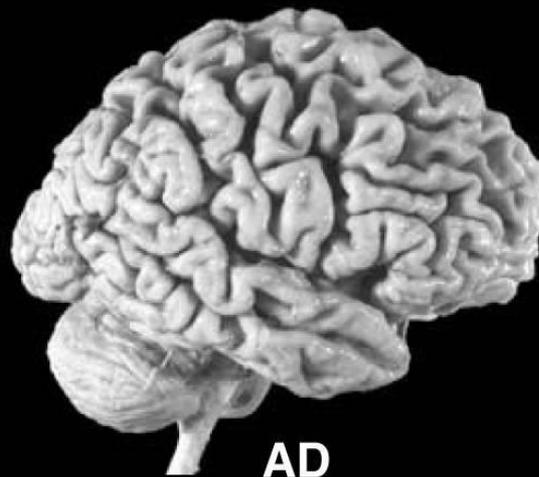
E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Episode, Schizophrenia).

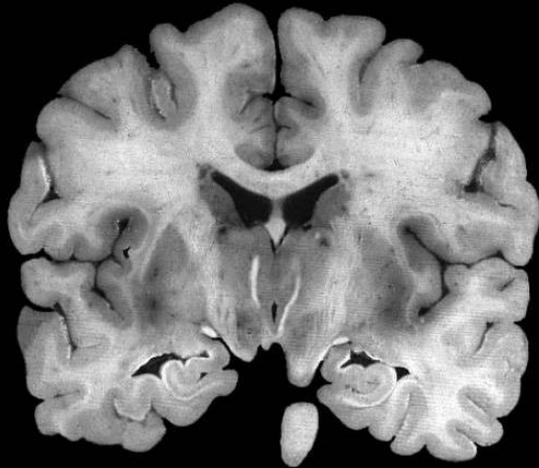
Brain Atrophy in Advanced Alzheimer's Disease



Normal



AD



CSF biomarkers

- Despite significant research efforts directed towards a better understanding of the mechanisms underlying HIV neuropathogenesis, definitive causal pathophysiology of HAND and thus effective prevention or treatment remain elusive
- Controversies exist as to whether milder forms of memory and cognitive impairments detected on neuropsychometric tests have any true clinical or prognostic significance, and there remains uncertainty as to whether HIV replication (or, indeed, HIV driven neuroinflammation) at primary, or during chronic infection is the cause
- Despite viral suppression in plasma below the limit of detectability, replication may rarely occur within the cerebrospinal fluid (CSF).

- There is growing interest in the field of CSF biomarkers for neuronal injury and associated cognitive impairment in PLWH.
- CSF Neurofilament light chain (NFL) has emerged as a sensitive marker for assessing ongoing axonal damage in HIV infected patients.
- It has previously been found that CSF NFL can predict severe neurocognitive impairment.
- Impairment of BBB with simultaneously raised levels of CSF neopterin and CSF NFL give further support to the existence of neuroinflammation and axonal injury in untreated HIV.
- High levels in treated HIV patients might be important in HAND evaluation

CSF biomarkers in other patients with Alzheimer's Disease

- In PLWH who have significant cognitive decline CSF analysis may help diagnose other conditions such as AD when used alongside MRI and PET scanning
- CSF is measured for

CSF TOTAL TAU reference range 146-595pg/ml

CSF A-BETA 1-42 reference range 627-1322pg/ml

CSF TAU/ABETA RATIO reference range <1.00

CSF PHOSPHORYLATED TAU reference range 24-68pg/ml

The analysis of these figures in a study done at the National Hospital for Neurology and Neurosurgery showed that the combination of an A-Beta 1-42 < 450 pg/ml with a Tau AB ratio of >1 and a phosphorylated Tau of >62 gave a sensitivity of 68.5% and a specificity of 86.9% and a diagnosis of Alzheimer's disease.

The lumbar puncture in a patient presenting with cognitive decline

In a patient with HIV infection that is well controlled who presents with non mood related cognitive decline, after MRI should have a lumbar puncture that a lumbar puncture. The opening pressure should be measured and the CSF should be sent for:

M,C &S

Protein and glucose (WITH A SERUM GLUCOSE)

OCB (WITH MATCHED SERUM)

Viral PCR for common viruses – enterovirus, HSV, VZV

HIV viral load with matched serum for viral load

Cerebrospinal fluid (CSF) amyloid- β 1–42, tau, and phosphorylated tau

MMSE

- 24/30 suggestive of dementia (sens 87%, spec 82%)
- Not sensitive for MCI
- The MMSE may be spuriously low in people with low educational level, low socioeconomic status, poor language skills, illiteracy and impaired vision
- Not sensitive in people with higher educational background
- I prefer to do Addenbrooke's cognitive assessment

Addenbrooke's cognitive assessment - ACE

- Attention

Attention is tested by asking the patient for the date including the season and the current location; repeating back three simple words; and serial subtraction.

- Memory

Memory is tested by asking the patient to recall the three words previously repeated; memorizing and recalling a fictional name and address; and recalling widely-known historical facts.

- Fluency

Fluency is tested by asking the patient to say as many words as they can think of starting with a specified letter within one minute; and naming as many animals as they can think of in one minute.

- Language

Language is tested by asking the patient to complete a set of sequenced physical commands using a pencil and piece of paper such as "place the paper on top of the pencil"; to write two grammatically-complete sentences; to repeat several polysyllabic words and two short proverbs; to name the objects shown in 12 line drawings, and answer contextual questions about some of the objects; and to read aloud five commonly-mispronounced words.

- Visuospatial

Visuospatial abilities are tested by asking the patient to copy two diagrams; to draw a clock face with the hands set at a specified time; to count sets of dots; and to recognise four letters which are partially obscured.

Scoring

- The results of each activity are scored to give a total score out of 100 (18 points for attention, 26 for memory, 14 for fluency, 26 for language). A score of 88 and above is considered normal; below 83 is abnormal; and between 83 and 87 is inconclusive.

Features in J.P that were unusual

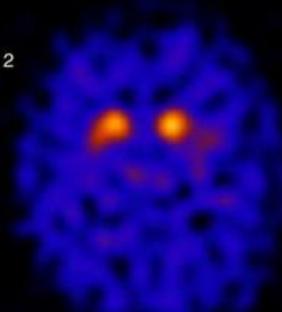
- Cogwheeling
- Hallucinations
- Dementia with Lewy Bodies

DAT scan abnormal

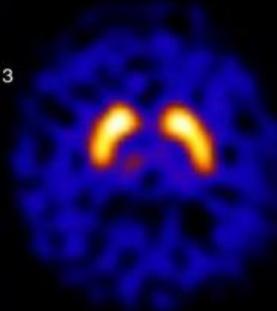
Case 1



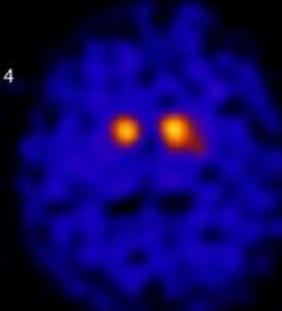
Case 2



Case 3



Case 4



AD

DLB

Conclusions

- HAND in patients with well controlled HIV is rare
- We are likely to see more in the way of vascular cognitive impairment and AD with the ageing population.
- Neuropsychology, mood assessment, MRI and lumbar puncture are the most important tests in evaluating cognitive impairment.
- Brain PET and DAT scans might be helpful in a subset of patients