

Neuropsychiatric Complexities in the HIV Patient – Clinical Challenges beyond Neurocognitive Disorders

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Abstract

Objective: To illustrate clinical challenges, explore existing literature and identify knowledge gaps in the management of neuropsychiatric issues beyond neurocognitive disorders in HIV patients.

Methods: Three case vignettes from a consultation-liaison psychiatry setting in a general hospital were collated and summarised into a case series. Clinical questions were identified from each vignette and pertinent literature reviewed to aid a further discussion of management issues.

Results: The first case vignette discusses the potential of a multi-dimensional approach to the formulation of a HIV patient with emergent psychiatric and cognitive symptoms. In the second, pharmacological treatment of a HIV patient with a severe manic relapse of Bipolar 1 Disorder and active TB disease is discussed. Lastly, the collective effects of severe Traumatic Brain Injury (TBI) and HIV infection superimposed on that of an ageing brain are described. Iatrogenic risks of polypharmacy in an elderly HIV patient are further explored.

Conclusion: The practical aspects of clinical challenges regarding the management of HIV patients are multi-fold and most apparent in a real-world setting. Existing literature does not yet adequately address the diagnostic dilemmas and pharmacological complexities faced. The management of other neuropsychiatric manifestations in a HIV patient remains a crucial field to be explored.

Keywords: HIV infection; Neuropsychiatric disorder; HIV psychiatry

Background

Modern antiretroviral treatments have greatly improved the survival of patients with HIV, resulting in the increasing emergence of a new group of patients that clinicians now have to manage using a chronic disease approach. This group of patients age doubly, both in terms of being at an increased mean age and also as a result of premature ageing from the HIV infection itself, thus placing cognitive problems at the forefront of clinical management [1,2], much like the geriatric patient. Indeed, much literature has been published on milder forms of cognitive impairment aside from HIV-Associated Dementia where there are deficits in cognitive domains such as executive functioning, episodic memory, speed of information processing and motor skills various deficits, culminating in research criteria for the different forms of HIV-Associated Neurocognitive Disorder (HAND) [3] as well as expert consensus guidelines for diagnosis and treatment [4]. General hospital psychiatrists have found that the emphasis for HIV care has shifted to detecting and managing this chronic neurological complication, and rightly so, for there is good evidence that HAND adversely impacts medication adherence, functional outcomes and quality of life [5]. However, an area where existing literature has been inadequate, is the discussion of the real-world clinical challenges of managing an HIV patient with neuropsychiatric complexities including and extending beyond cognitive issues and resulting in difficulties applying the recommended guidelines.

An increased life expectancy also portends the fact that the general hospital psychiatrist needs to manage these patients' pre-existing non-HIV related co-morbidities [6,7]. These can run the gamut from neurological complications of common diseases such as diabetes mellitus and hypertension to neurological or psychiatric illnesses pre-dating the HIV infection. In addition with the passing of time, the HIV patient further accumulates other co-morbidities that add on to a growing list of issues, such as neurodegenerative diseases and neurotrauma.

Challenges such as complex pharmacological interactions, differential diagnoses, interaction of comorbidities and non-classical presentations of common disorders have now become forefront issues psychiatrists have to grapple with, while the management of AIDS-related symptoms take a momentary backseat. In this paper, we discuss three cases to demonstrate the complex clinical challenges faced in the psychiatric consultation-liaison setting of a general hospital, where co-morbidities such as bipolar disorder, traumatic brain injury and temporal lobe epilepsy interplay with the delicate balance of managing a patient's HIV illness.

Case 1

The first case is that of a 56 years old Chinese male. He has 3 years of formal education and had been retrenched a year ago as a printing machine operator. Significant medical history included encephalitis in 2002, temporal lobe epilepsy diagnosed in 2007, hypertension and dyslipidemia. There was no past psychiatric history. He was diagnosed with HIV in 2008 after presenting with Pneumocystis Carinii Pneumonia (PCP) and his CD4 count then was <10. In 2009, he was treated for Central Nervous System (CNS) Tuberculosis (TB).

In 2014, he presented with cognitive and functional decline over 6 months as well as worsening seizure frequency, increasing from

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monthly episodes to fortnightly. Of note, there was marked slowness in recall of information and in verbal and motor responses, resulting in poor work performance and impaired driving ability. There was also increased emotionality where he would cry easily. His antiretroviral (ART) regime consisted of Zidovudine, Lamivudine and Efavirenz which gave a total CNS Penetration Effectiveness (CPE) score of 9 [8]. Symptoms of depression could not be elicited due to marked slowness and reduced verbal output.

On Mental State Examination (MSE), he was a neatly dressed middle-aged Chinese male who was unable to describe his mood and had blunted affect. However, when asked if he felt that life was meaningless, he suddenly burst into tears. There was increased latency of response and poverty of speech. There were no formal thought disorders, perceptual abnormalities or suicidal ideation. On cognitive testing, Mini Metal State Examination (MMSE) score was 12/28 and Montreal Cognitive Assessment (MOCA) score was 15/30, showing deficits of attention, memory and executive functioning. International HIV Dementia Scale was not done as he refused further testing. Neurological examination only showed apraxia on the left. Laboratory testing showed a CD4 count of 477 and undetectable HIV viral load. Magnetic Resonance Imaging (MRI) of the brain showed bilateral chronic lacunar infarcts and microhaemorrhages, small vessel disease, asymmetric right hippocampal atrophy and mild diffuse involuntional changes. Lumbar puncture for cerebrospinal fluid viral load measurement was unsuccessful despite fluoroscopic guidance.

He was started on Memantine by his neurologist but had to stop due to worsening seizure frequency. Interestingly, a therapeutic trial of Escitalopram for Depression resulted in not only improvements in terms of emotional dyscontrol, but also with seizure frequency and overall functioning. However there were no improvements in cognitive scores.

This case illustrates the challenges with differential diagnoses in a complex neuro-psychiatric presentation of a HIV patient. The differential diagnoses considered in this case were that of Depressive Disorder, Vascular Depression, Alzheimer's Dementia, Vascular Dementia and HAND. His risk factors for HAND were his low levels of education, low nadir CD4, history of an opportunistic infection in the CNS and presence of possibly neuro-toxic medications [9]. Depressive disorders [10], vascular lesions in the brain and vascular risk factors [11] are all highly prevalent in the HIV population. Accelerated aging in HIV also raises the possibility of neurodegenerative conditions like Alzheimer's dementia [12] especially since hippocampal atrophy and cerebral involution was present. The MRI findings may also indicate an element of emotional lability after stroke [13], in addition to asymmetrical hippocampal atrophy possibly from the effects of encephalitis and epilepsy. His clinical status also made full neuropsychological testing for diagnostic clarification unfeasible. As demonstrated in this case, there exists patients for whom guidelines cannot be applied and an alternative diagnostic approach is necessary. Consideration of a multi-modal picture such as new-onset psychiatric and/or age-related co-morbidities superimposed on that of pre-existing neurological disease accounts for the possibility that the presentation of HIV-associated diseases can be confounded. In addition, a diagnostic trial of antidepressants can be helpful to differentiate pseudo-dementia from dementia and delineate the extent of dual diagnoses.

Case 2

The second case is that of a 41 year old Chinese male with a background history of Bipolar I Disorder. He had previously required Electroconvulsive Therapy (ECT) for mania, but was now stable on a

maintenance dose of Quetiapine 400 mg nocte and Valproic Acid 500 mg twice daily. He was diagnosed with HIV in 2015 after presenting with disseminated TB and a likely tuberculous lesion in the right cerebellum. At time of diagnosis, his CD4 count was <20 and viral load 246,300 copies. He was started on high-dose steroids to reduce the mass effect of the cerebellar lesion and also TB treatment with Rifampicin, Isoniazid, Ethambutol and Pyrazinamide. In addition, he required Clarithromycin prophylaxis for atypical mycobacterial infection. His ART regime included Tenofovir, Lamivudine and Ritonavir-boosted Atazanavir which gave a total CPE score of 5. In the course of his hospitalization however, he suffered a manic relapse and bit a nurse in his agitated state, requiring physical and chemical restraints for himself and necessitating post-exposure HIV prophylaxis for the victim.

On MSE, he was a middle-aged Chinese male of small build. He was restless and animated, with elated mood and affect. He had a grandiose delusion of possessing healing powers with martial arts and of being able to heal himself of HIV. He denied hallucinations in any sensory modality. Pressured speech and flight of ideas were observed. There were no focal neurological signs on physical examination.

This case illustrates the differential diagnoses of mania in a HIV-positive patient and the pharmacological considerations in the acute management of a patient who is experiencing relapses of his multiple diagnoses. Given the advanced state of HIV at the point of diagnosis, the phenomenon of AIDS mania [14,15] is certainly a diagnostic consideration, with the cerebellar lesion and exposure to a potent steroid as contributing organic factors. However, given his pre-existing history of Bipolar Disorder I, it is also likely that his manic relapse had been precipitated by stress from his physical illnesses and the prolonged hospitalization.

Perhaps more importantly, reduced plasma levels of his maintenance psychotropics may have contributed to his relapse due to drug-drug interactions with Rifampicin and Clarithromycin, both having potent effects on hepatic enzymes [16,17].

Furthermore, pharmacological considerations for treatment of Bipolar Disorder in the HIV patient span across not only the acute phase of mania but also during long-term maintenance therapy. TB medications, ARTs and other additional medications, in this case, Clarithromycin, have to be checked for drug-drug interactions with acute phase and maintenance psychotropics. At the same time, it is essential to keep in mind that treatment for TB and prophylaxis for atypical mycobacterium are both time-limited treatments that will be stopped at defined points in the course of illness. When the courses of antibiotics have been completed, the doses of both psychotropics as well as ARTs will have to be decreased in order to avoid drug toxicity. Hence, the clinician's choice of ARTs will have to be carefully considered, especially since the patient is still relatively ART-naïve at this point. There is a role here for the psychiatrist to collaborate with the HIV physician and advocate for the patient's mental health care needs. ECT is an option for a manic patient who does not respond adequately to psychotropics, but for this patient, the presence of the cerebellar lesion may be a contraindication for ECT [18]. In view of the potential risks of harm to self and others during a manic relapse, combination therapy of psychotropics or doses exceeding the maximum recommended dose may also have to be used with the appropriate medical monitoring [19].

Case 3

The third case is that of a 64 year old Chinese male, unemployed and not formally educated, with a background medical history of

Challenges	Recommendations
Diagnostic Challenges <ul style="list-style-type: none"> - Lack of accurate psychiatric history due to patients' poor insight - Incomplete neuropsychological testing due to poor clinical status - Lack of spinal fluid analysis - Confounders of pre-existing disease on top of new-onset disease 	Diagnostic trial of psychotropics
	Formulation of diagnoses considering multiple aetiologies
	Use clinician-rated scales as opposed to patient-rated scales
	Longitudinal observation and regular reviews of diagnoses at appropriate intervals
Pharmacological Interactions <ul style="list-style-type: none"> - Drug-drug pharmacokinetics - Drug-disease considerations - Drug-brain effects - Aging effects on brain - Aging effects on pharmacodynamics - Rationale for polypharmacy - Acute phase treatment vs. long-term maintenance treatment 	Consider interactions with possible need for maintenance psychotropics when deciding on initial choice of anti-retroviral therapy
	Anticipating psychotropic changes when moving between acute and maintenance phases of psychiatric illness
	Setting time points for reassessment of pharmacological regime at turning points of illness
	Watch for metabolic and cardiovascular side-effects of psychotropics especially in the older person
	Be mindful of cognitive reserve and its impact on illness and drug effects
	Maintain close collaboration of HIV physician with psychiatrist

Table 1: Recommendations for overcoming challenges in the management of psychiatric comorbidities in HIV [32-39].

hypertension and old strokes. At time of HIV diagnosis, his CD4 count was 131 and viral load was 164 copies. This had improved to a CD4 count of 176 and undetectable viral load after 3 months of ART consisting of Abacavir, Lamivudine and Efavirenz. 6 months after diagnosis, he was involved in a road traffic accident as a helmetless motorcyclist and suffered a severe Traumatic Brain Injury (TBI) and skull fractures. Glasgow Coma Scale (GCS) was 7 at the accident scene and 9 on arrival at the Emergency Department. Computed Tomography (CT) of the head showed left subdural haemorrhage, right extradural haemorrhage, pneumocephalus from skull and facial fractures and diffuse axonal injury. He also had several other musculoskeletal injuries and was managed in the neurosurgical intensive care unit with intracranial pressure monitoring and intravenous mannitol.

Upon transfer to the inpatient neurorehabilitation unit, he remained in post-traumatic amnesia [20] and continued to have severe sleep-wake disturbance and bouts of agitation. In the day he required one-to-one nursing care and constant distraction through engagement with a variety of activities. There were episodes of severe aggression resulting in damage to objects and furniture. High-doses of Olanzapine were used for tranquilization in addition to Lorazepam and Zopiclone for night sedation, but to no avail. Furthermore, antiretroviral treatment was changed from Efavirenz to Ritonavir-boosted Atazanavir to reduce possible neurotoxicity [21,22]. His convalescence was unfortunately complicated by a fall with further head injury as well as a myocardial infarction.

MSE showed an elderly Chinese male who was disoriented to time, place and person. He was inattentive and constantly asking to go home or for his son to come. He was restless and when left alone, would struggle against his restraints and shout for attention. Abnormalities of mood and perception could not be elicited. In the wake of his fall and cardiovascular event, all antipsychotics and sedatives were temporarily stopped to minimise the risks of further complications [23,24]. As he progressed, psychotropics (Olanzapine, Melatonin Prolonged Release and Methylphenidate) were gradually reintroduced at low doses to help regulate his sleep-wake cycle and agitation. He was eventually discharged to a nursing home and as of the latest outpatient review, it was reported that his bouts of agitation and sleep-wake disturbance had settled. Psychotropics were consequently down-titrated with the eventual intention for tailing off.

This case is used to discuss the combined effects of TBI and HIV on the brain of an elderly person, as well as unique pharmacological considerations. There has been one study so far that showed that a TBI increases the risk of neurocognitive impairment in HIV [25]. This

study has not been replicated. This patient has risk factors for HAND (advanced age, low educational attainment, low nadir CD4) [9]. His cognitive reserve is also likely to have been reduced since he would be regarded as an “elderly” patient due to the effects of accelerated aging in HIV [1,2]. The risk associated with the use of atypical antipsychotics for behavioural difficulties in the elderly with dementia has been well-documented and should be extrapolated to this case as well [26]. Perhaps, the slightly older HIV patient is equally vulnerable to cardiovascular morbidity and mortality as the geriatric patient. Similarly, the risks of falls associated with the use of benzodiazepines in the elderly should also be a concern [27]. Furthermore, the use of benzodiazepines has the potential to hinder cognitive recovery in this patient [28]. However, pharmacological options for regulating sleep-wake disturbances are, in reality, limited. Nevertheless, this was one of the more important treatment goals for him as it caused extreme difficulties in nursing care. The potential neurotoxicity from Efavirenz should also be considered in this patient especially since his cognitive reserve is severely reduced [21,22].

Discussion and Conclusion

A literature search on the neuropsychiatry of HIV reveals an emphasis on the diagnosis and management of neurocognitive impairment in HIV [29]. Full neuropsychological testing is the recommended standard for diagnosis while considering psychiatric differential diagnoses concurrently [3,4]. However, existing literature does not adequately address the practical challenges and complexities in clinical practice where many patients are unable to undergo neuropsychological testing. Most studies were conducted among stable outpatients, thus missing out on the most complex patients who are usually in the inpatient setting. It can be seen from these 3 cases that the presence of comorbid issues and atypical presentations necessitate detailed and comprehensive neurological assessments and psychiatric formulations. The use of screening tools such as mood and anxiety questionnaires as recommended in expert consensus guidelines would have been insufficient. These cases also highlight the fact that there are instances when HAND cannot be easily or confidently diagnosed.

Furthermore, literature on the pharmacological complexities in the treatment of medical and psychiatric comorbidities of HIV patients remains a relatively unreported field. As can be seen in the cases discussed, the general hospital psychiatrist needs to account for the complex interplay of drug-drug, drug-disease, drug-brain and disease-brain interactions. Table 1 illustrates several recommendations for overcoming this diagnostic and pharmacological challenges.

As aging with HIV becomes commonplace, it is inevitable that psychiatrists will be facing more of such complex patients to manage especially since available studies have reported a higher prevalence rate of psychiatric and medical co-morbidities in HIV patients [30,31]. Specifically-trained HIV psychiatrists are few in number, so the onus is on the general hospital psychiatrist to combine up-to-date knowledge with clinical acumen and sound clinical practice so as to provide these complex patients with the best available care.

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