Cognitive Disorders in People Living with HIV Disease

INTRODUCTION

Approximately 60% of people living with HIV will develop cognitive difficulties over the course of the illness. According to McArthur and others (1993), 15% to 19% will develop cognitive problems severe enough to meet criteria for dementia in that the cognitive difficulties adversely affect their everyday work and social function. In 1991, the American Academy of Neurology adopted the nomenclature HIV-1–associated cognitive/motor complex (HACM) to describe the neurobehavioural disorders that occur with HIV infection. For about 4% of HIV-infected people, HACM will be their AIDS-defining diagnosis. Given the prevalence of cognitive disorders in people living with HIV, it is essential that practitioners accurately assess any changes in mental status.

The human immunodeficiency virus enters the central nervous system shortly after infection. It has a predilection for the subcortical brain areas, where it can cause cell injury, cell dysfunction, or cell death. People with neurocognitive complications associated with HIV disease present with a complex of affective, behavioural, cognitive, and motor findings. The signs and symptoms that result can be attributed to the intricate interactions between HIV (in particular, HIV-strain characteristics that increase central nervous system infection) and other factors, including the person’s systemic condition, biological vulnerability to
cognitive disorders, premorbid primary psychiatric and substance-related disorders, the neuropsychiatric effects of medications used to treat HIV disease and its complications, and the psychological impact of a life-threatening illness. This interplay of organic and functional, primary and secondary factors can be challenging to understand. Diagnosis must be grounded in a thorough history and careful psychiatric, mental status, and neurologic examination. Any assessment must consider the patient’s clinical stage as well as laboratory markers of immune dysfunction and viral burden.

In diagnosing and managing HACM and other cognitive disorders associated with HIV disease, the psychiatrist should work closely with the treating internist, primary care physician, and neurologist. Psycho-pharmacologic management must involve treating both the symptomatic condition and the underlying disease process.

What are the characteristics of HACM?

HACM comprises two types of neurobehavioural disorders:
- a dementia with neuropsychological impairment that is severe enough to influence activities of daily living markedly, referred to as HIV-1–associated dementia complex (HADC). The DSM-IV diagnosis (American Psychiatric Association 1994) for this condition is Dementia due to HIV disease.
- a milder disorder with less severe impairment, referred to as HIV-1–associated minor cognitive/motor disorder (MCMD).

Severe HACM is progressive, but the milder disorder is often stable. People with the milder disorder often experience no progressive deterioration and only mild transient worsening during times when they are ill. According to the Dana Consortium on Therapy for HIV Dementia and Related Cognitive Disorders (1996), it remains unclear whether HIV-1–associated MCMD and HADC are two distinct entities or a single continuous entity differentiated only by severity.

HACM is characterized by:
- a progressive slowing of cognitive functions, including concentration and attention, memory, new learning, sequencing and problem solving, and executive function. Higher cortical functions are usually preserved. Aphasia and agnosia are rare, except in end-stage disease.
- behavioural changes, which mainly take the form of apathy, loss of motivation, anergia, fatigue, and social withdrawal. Patients may also suffer from depressed mood, but depression may be differentiated from HACM by the qualitative affect of sadness rather than apathy alone. Mania, hypomania, and disinhibition syndromes are less common but have been reported in association with advanced systemic HIV disease and as a side effect of some medications used to treat HIV disease (for example, lamivudine [3TC] and zidovudine [AZT]). (See Chapter 4 on mood disorders.)
- motor changes, including psychomotor slowing, clumsiness, unsteadiness of gait, hyperreflexia, deficits in fine
motor speed and control, and deterioration of handwriting.

What are the risk factors for HACM?

Risk factors that correlate with HACM in adults include older age, lower educational achievement, anemia, and more constitutional symptoms before the onset of clinically defined AIDS. The prevalence of cognitive dysfunction secondary to HIV infection parallels the progression of systemic HIV disease. Cognitive deficits are least common in people with asymptomatic HIV infection and most common in patients with an AIDS-defining condition. After the onset of an AIDS-defining condition, the annual incidence of onset of severe HACM is about 7%. Both HADC and MCMD correlate independently with activities of daily living.

What is the prevalence of HACM?

Figure 2.1, based on a study conducted by the San Diego HIV Neurobehavioral Research Center, illustrates the increasing prevalence of global neuropsychological impairment with each successive stage of HIV disease. These rates of neuropsychological impairment correspond well to the median rates of impairment reported in recent reviews of the literature by Heaton and others (1996) and White and others (1995).

Similar patterns of cognitive deficits (that is, patchy deficits in several cognitive domains) have been seen among both gay and bisexual men and injection drug users. The prevalence of dementia in the two groups may differ depending on previous brain insults (for example, exposure to toxic substances and head injury).

The pathophysiological mechanisms underlying HACM are still being investigated, but the presence of HIV is generally considered to be the force that drives HACM. Both the direct effect of HIV on the brain and bystander effects from chronic inflammatory response to the presence of HIV (for example,

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**Table 2.1. American Academy of Neurology criteria for HACM**

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<tr>
<th>Criterion</th>
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<td>1. Acquired abnormality in at least two of the following cognitive abilities (present for ≥ one month):</td>
<td>attention/concentration, abstraction/reasoning, memory learning, speed of processing, visuospatial skills, speech/language</td>
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<td>a) Decline verified by history and mental status examination. When possible, history should be obtained by an informant, and examination supplemented by neuropsychological testing.</td>
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<td>b) Cognitive dysfunction causing impairment of work or activities of daily living; impairment not attributable solely to severe systemic illness.</td>
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<td>2. At least one of the following:</td>
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<td>a) Acquired abnormality in motor function or performance verified by physical examination, neuropsychological tests, or both.</td>
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<td>b) Decline in motivation or emotional control or change in social behaviour, characterized by any of the following:</td>
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<td>Apathy, inertia, irritability, emotional lability, or new-onset impaired judgement, characterized by socially inappropriate behaviour or disinhibition</td>
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<td>3. Absence of clouding of consciousness during a period long enough to establish the presence of #1</td>
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<td>4. Evidence for another etiology, including active central nervous system opportunistic infections or malignancy, psychiatric disorders (e.g., depressive disorders), active substance abuse, or acute or chronic substance withdrawal, must be ruled out by history, physical and psychiatric examination, and appropriate laboratory and radiologic tests.</td>
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cytokine liberation) are presumed to play roles in the process.

**What are the criteria for diagnosing HACM?**

The diagnostic criteria for HACM are listed in Table 2.1. To be diagnosed with HACM, a patient must have a verifiable change in cognitive ability and a deficit in either motor or affective and behavioural function that affects the person’s ability to work or perform other activities of daily living. The change must persist for at least one month and cannot be attributed to another cause.

The severity of cognitive changes is assessed using the Memorial Sloan-Kettering (MSK) clinical rating system (Table 2.2). Patients with minimal- or mild-severity HACM (MSK stages 0.5 or 1) experience limited cognitive deficits, which do not preclude their ability to manage daily social and occupational tasks and do not meet the impairment criteria for dementia. Patients with stage 1 HACM (MCMD) do, however, have demonstrable neurocognitive difficulties, and studies by Heaton and others (1995) and Albert and others (1995) suggest that they have higher rates of work difficulties and disability than patients with a similar stage of HIV disease without cognitive deficits. Those with more severe HACM (that is, MSK stages ≥ 2, which meet the criteria for HADC) experience much more serious and debilitating losses.

**What is the course of illness?**

HACM generally progresses slowly over time, with patients experiencing temporary or transient cognitive losses during periods of infection or metabolic disturbance. Patients with mild HACM often remain stable, with no progressive deterioration or only mild, transient worsening of symptoms during periods of illness.

Rapid progression appears to be related to the patient’s overall systemic health and immune function. Patients who are most immunocompromised and systemically unwell are at the highest risk of rapid progression.

Any abrupt changes in mental status (such as rapid deterioration, new-onset focal neurologic findings, seizures, psychosis, or mania) should be investigated for causes other than or in addition to HACM.

**CASE STUDY**

**HIV-1-ASSOCIATED COGNITIVE/MOTOR COMPLEX**

Ravi is a 50-year-old gay male currently employed as a vice-president of a large company. Over a three-month period, his employer has noticed a decline in his work performance. Ravi is no longer able to remember appointments...
and agendas as he once did. He acknowledges that his memory has been less sharp over the past year. He says he is unable to concentrate in meetings and feels two steps behind his usual mental pace. He is having difficulty learning a new computer software package and remembering the plot of the latest book he is reading.

Ravi reports that he is frequently fatigued, has less energy, and is unenthused about his work or other activities. He has lost 3.6 kg in the past year and has a difficult time falling asleep. He is less interested in socializing with friends. His partner says that he is uninvolved in home chores, irritable, and indecisive. When pushed by his partner, Ravi can take pleasure in activities but is reluctant to participate in most things he enjoyed in the past. His partner complains that he is slower and frequently clumsy.

Ravi reports feeling frustrated rather than sad. He has been drinking more alcohol at night and using over-the-counter sleep preparations without relief. He has no suicidal ideation or intent. He has no personal or family psychiatric history.

He had one episode of Pneumocystis carinii pneumonia (PCP) two years earlier, but is currently systemically well, with only mild oral candidiasis. His medications include AZT 100 mg three times a day and didanosine (ddI) 200 mg twice daily as antiretroviral treatment; his physician will soon be adding a protease inhibitor to his treatment regimen. His most recent CD4 lymphocyte count was 90.

What elements in this history are important in establishing the diagnosis?

The important diagnostic elements are:

- cognitive, affective, and motor complaints in the midst of significant immune suppression
- a clinical diagnosis of AIDS, based on a past episode of PCP, even though the patient is currently systemically stable
- a pattern of cognitive deficits consistent with a slowly progressive decline in memory, concentration, new learning, and speed of processing
- behaviour that is apathetic, amotivated, withdrawn, and at times irritable, but with no particular feelings of sadness
- slow and, at times, clumsy motor functions but no focal neurologic symptoms

By history, the presentation is very typical of HACM, but because of this patient’s immune suppression, other causes of cognitive dysfunction must be considered.

What is the differential diagnosis?

The differential diagnoses that should be considered are:

- **Infections:**
  - HACM, cognitive decline secondary to HIV infection, and its direct and indirect consequences on the brain
  - other secondary opportunistic infections for which this patient is at risk secondary to immune dysfunction, including toxoplasmosis, progressive multifocal leukoencephalopathy (PML),

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**Early Nomenclature for HACM**

The following early nomenclature may still be used in certain settings.

- **HIV-1–Associated Dementia Complex**
  - HIV-1-associated dementia
  - AIDS dementia complex
  - HIV encephalopathy
  - Subacute encephalitis
  - AIDS-related dementia

- **HIV-1–Associated Minor Cognitive/Motor Complex**
  - HIV-1-associated mild neurocognitive disorder
  - HIV-1-associated neurocognitive disorder
  - HIV-associated neurobehavioural abnormalities
neurosyphilis, cytomegalovirus (CMV) encephalitis, brain abscess

- other secondary opportunistic infections for which this patient is at risk secondary to immune dysfunction and which primarily affect meningeal structures, including cryptococcal meningitis and tuberculous meningitis

- **Tumours:** specifically primary cerebral lymphoma, which is associated with advanced HIV disease and, more rarely, metastatic Kaposi’s sarcoma

- **Metabolic disorders, endocrinopathies, and vitamin deficiencies:** including hypothyroidism, B₁₂ deficiency, hypogonadism, malnutrition, and anemia

- **Vascular diseases:** including anemia, hypotension, and vasculitides

- **Drug intoxications and substance-related disorders:** including withdrawal states and medication side effects

- **Primary psychiatric disorders:** specifically major depression

Hypoxia can result from several of these conditions and must be considered in the differential diagnosis.

No single investigation or piece of information can lead to a diagnosis of HACM. Instead, the practitioner must consider data from systemic, neurologic, and psychiatric examination, as well as ancillary investigations.

When the patient’s CD4 lymphocyte count is below 200, the practitioner must consider secondary opportunistic infections and tumours. The course of illness described in this case, however, which has developed over several months, is more consistent with HACM, endocrinopathy or metabolic disturbance, or psychiatric disorder than with a secondary infection:

- Toxoplasmosis, lymphoma, cryptococcal meningitis, CMV, and PML are usually acute in their onset and progress rapidly, although they can take a more indolent course.

- Toxoplasmosis, cryptococcal meningitis, and CMV are generally accompanied by signs of systemic illness, such as headache, fever, and decreased level of consciousness.

- *Cryptococcus* generally presents with some meningeal signs and symptoms, although in some cases, the only symptom is headache.

- CMV encephalitis is rare in people with CD4 counts >100 and is also rare in the absence of other sites (retina, colon) of CMV infection.

- Focal signs on neurologic examination are most commonly seen in toxoplasmosis, lymphoma, and PML.

Ravi’s neurologic examination revealed brisk reflexes bilaterally, mild extrapyramidal signs, generalized psychomotor slowing and clumsiness, but no focal signs. Psychiatric examination revealed an absence of personal and family psychiatric history but a pattern of substance use, including alcohol and hypnotics, which may affect cognitive function.

**What other investigations are necessary?**

Hematological and biochemical investigations, anatomic brain imaging, cerebrospinal fluid (CSF) examination, and neuro-psychological testing will help support the findings of clinical examination and exclude other causes of central nervous system dysfunction.

- **The treating physician should order investigational blood work,** including hemoglobin, glucose, electrolytes, calcium, albumin, magnesium, vitamin B₁₂, thyroid-stimulating hormone, free testosterone, and VDRL to exclude metabolic derangements, vitamin deficiencies, endocrinopathies, and neurosyphilis. A negative serum VDRL does not exclude neurosyphilis from the differential diagnosis, so that if this condition is suspected clinically, based on a history of syphilis that may have been undertreated, or if the patient has a positive serum FTA-antibody confirmatory test indicating past syphilitic infection, further investigation, including a lumbar puncture, should be conducted.

- **The physician should measure levels of psychoactive drugs,** including anticonvulsants, sedatives, narcotics, and antidepressants, as well as alcohol, if either chronic or acute intoxication is suspected. The physician should also assess clinically for anticholinergic intoxication.

- **The physician should use anatomic brain imaging techniques to detect other causes of central nervous system dysfunction,** such as mass or vascular lesions due to toxoplasmic encephalitis, lymphoma, or stroke, which may complicate the course of HIV-1 disease. Brain imaging should always be done for patients with focal neurologic signs or with rapidly progressive deterioration, decreased level of
alertness, or new-onset mental status change such as seizure, mania, or psychosis in the course of HIV disease. (In Ravi’s case, where there were no focal findings and a clinical picture consistent with HACM, anatomic brain imaging is less necessary.) Brain imaging techniques do not reliably detect early changes of HACM nor do they show a high degree of specificity in clinical staging. Magnetic resonance imaging (MRI) is more specific and sensitive than computerized tomography (CT). The most common finding on both is cerebral atrophy and ventricular enlargement, with a pattern of combined central and cortical atrophy. MRI may also detect patchy T2-weighted white matter lesions and is more sensitive than CT in detecting regional atrophic changes, particularly in the subcortical structures. The CT done on Ravi confirmed the absence of focal brain pathology and showed moderate atrophy and ventricular dilatation. The physician should use a CSF examination primarily to exclude other conditions that may lead to mental status changes, including opportunistic infections (CMV, Cryptococcus), tumours, and syphilis. In HACM alone, a CSF examination may show pleocytosis, elevated immunoglobulin-G, oligoclonal bands, and increased protein. All are nonspecific and do not correlate well with clinical severity. Research investigations, including measures of immune activation such as increased CSF β2-microglobulin or quinolinic acid levels and measures of increased levels of CSF viral load, have been shown to correlate with clinical severity of cognitive decline and may develop into useful clinical staging tools in the future. With Ravi’s history highly suggestive of HACM—there being no history of syphilis, a negative serum VDRL and FTA-antibodies, no focal neurologic signs, and a negative serum cryptococcal serum antigen—the psychiatrist felt a lumbar puncture would add little to the diagnostic investigations, so it was not performed. In a patient for whom the index of suspicion for a meningeal process or neurosyphilis is high (positive serum VDRL and/or FTA-antibodies, past history of syphilis, and cranial nerve signs), a CSF examination is clearly warranted. The physician should consider ordering an electroencephalogram, which may show mild, nonspecific slowing, although it contributes little to the diagnostic evaluation unless a seizure disorder is clinically suspected. Functional neuroimaging with single photon emission computed tomography (SPECT), positron emission tomography (PET), or magnetic resonance spectroscopy (MRS) remain as research tools and do not yet significantly add to the diagnostic workup. The physician should conduct office-based mental status screening tests on all patients to document their mental status. The Folstein Mini-Mental State Examination (MMSE), which measures functions rarely impaired until advanced stages of HACM, is not sensitive to mild dysfunction and is therefore not a useful screening tool. Screening should incorporate tests of attention,
short-term memory, frontal executive function, and motor speed that will reliably identify patients with mild cognitive decline. The HIV Dementia Scale (HDS), which screens domains of memory, attention, psychomotor speed, and construction, has been developed as a useful and rapid screening examination. According to Power and others (1995), a validation analysis using an HDS score ≤ 10 to detect HIV-1–associated dementia was found to have a sensitivity of 80%, a specificity of 91%, and a positive predictive value of 78%. It is not yet widely used in psychiatry, however. Some clinicians use the Trail Making Test (A and B) as a brief screening tool for attention, concentration, speed of information processing, abstraction, cognitive flexibility, and executive skills. An abnormal score on these tests does not necessarily mean that the patient is functionally impaired. A consultation with an occupational therapist for assessment of activities of daily living can be enlightening in some situations.

What mental status screening and assessment tools should be used?

In the clinic where Ravi was assessed, the psychiatrist uses a mental status screening examination which he finds helpful in obtaining a global clinical impression of cognitive function but which has not been test-validated as a cognitive screening measure for HADC. The screening includes tests of orientation to person, place, time, digit span, four-word immediate registration and five-minute recall, serial sevens, Luria repetitive hand sequence manoeuvres, and Trail Making Tests (A and B). These tests are widely used by neurologists and psychologists, with whom psychiatrists interested in these tools can confer regarding their correct use. The psychiatrist notes the accuracy of the tasks, the speed of performance, and the qualitative manner with which the tasks are performed. As the screen has not been validated, it is not possible to include cut-off numbers for the evaluation.

Mental status examination conducted on Ravi revealed that he was fully oriented with a normal level of alertness. He could register four of four words immediately, but could recall only two of four words after five minutes. He could remember a digit span of five forward and three backward. He made only one error on serial sevens, but he was remarkably slow in his performance. He was clumsy with both hands in performing the Luria repetitive hand-sequencing movements and had difficulty repeating a complex sequential task. Using age- and education-adjusted norms, he scored in the bottom 25th percentile on the Trail Making Test (Part A) and in the bottom 10th percentile on Trail Making Test (Part B)—again displaying markedly slow performance indicative of diminished cognitive flexibility. This profile was consistent with HACM MSK stage 1, and it established a baseline for comparison with future examinations.

Ravi was interested in formal neuropsychological testing, which samples several cognitive domains, including attention, memory, motor speed, and cognitive flexibility, and is used to document cognitive deficits objectively and to characterize cognitive function. Baseline testing with longitudinal follow-up provides a means to monitor progression of cognitive dysfunction, measure clinical progression (more accurately than with cross-sectional testing alone), and evaluate responses to treatment interventions. (See Chapter 3 on neuropsychological testing.)

Could the patient’s symptoms be caused by major depression?

It is often difficult to differentiate HACM from a major depressive disorder. The two disorders frequently coexist, and both need to be treated appropriately. The presence of apathy, amotivation, and anergia (along with cognitive deficits consistent with HACM) and the absence of a qualitative subjective sense of sadness are more suggestive of HACM (or consequences of advanced systemic HIV disease) than a major depressive episode. Practitioners should rule out an organic etiology in patients living with advanced HIV disease before attributing the symptom complex to major depression alone.

In this patient, the absence of personal or family history of depression and his insistence that he did not feel sad suggest that the symptoms were caused by HACM. His symptom profile, however, including loss of interest, sleep disturbance, diminished energy, diminished concentration, decreased weight...
and appetite, and psychomotor slowing, did meet the criteria for a major depressive episode, so both disorders (HACM and major depression due to a medical condition) were considered in the diagnosis.

**Could the symptoms be caused by the substances being used?**

Alcohol, benzodiazepines, hypnotics, and narcotics can all diminish concentration and attention and contribute to cognitive decline.

In Ravi’s case, it is possible that alcohol and hypnotics were affecting his cognitive function, but as his condition continued to deteriorate despite stable substance use, it is unlikely that the substances account for all of his symptoms. It is possible that his sleep disorder was related to either HACM, major depression, or dDI use.

**Are there specific treatments for HACM?**

As HIV is believed to be the primary factor driving the progression of HACM, antiretroviral agents, particularly agents that penetrate the blood brain barrier, are considered first-line therapy. All antiretrovirals may be effective in treating HACM because of their benefit in improving the overall systemic condition, but AZT has thus far been shown to be the most effective in treating cognitive disorders because it has the greatest penetration of the blood brain barrier. The benefits of antiretrovirals in HACM can be divided into two main categories:

- the benefit in treating cognitive decline (that is, reversing and/or halting the progression of deficits) once deficits have emerged
- the benefit of early intervention with antiretrovirals as a means to prevent the emergence of HACM

Once deficits have emerged and the patient has been diagnosed with HADC, AZT monotherapy has been shown to improve neuropsychological performance. The benefits are generally short-lived, however, with efficacy being demonstrated for approximately 6 to 12 months before the HACM again begins to progress. According to Schmitt (1988) and Sidtis (1993), improvement in neuropsychological outcomes with AZT has been best demonstrated in adults with high daily doses (1500 to 2000 mg), but most patients cannot tolerate such high doses. Optimal dosing must balance the demonstrated benefit of higher doses against the negative impact on quality of life. From a practical standpoint, in an antiretroviral-naive patient presenting with HACM, an antiretroviral combination regimen that contains AZT 600 to 800 mg/day should be started and the cognitive function monitored.

In a patient already on antiretroviral medications presenting with HACM, it is important to reassess the antiretroviral regimen for a sufficient dose of AZT as well as for patient compliance. Increasing the AZT dose may help halt the progression; stavudine (d4T) may be used as a second-line antiretroviral that has some blood

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**Emerging treatment goals for HACM focus on achieving therapeutic levels in the CSF by using a combination of antiretrovirals to halt the progression of cognitive decline.**
brain barrier penetration, though studies demonstrating its efficacy are more limited.

Several studies suggest that early initiation of AZT, even at lower doses (300 to 600 mg/day), can help delay the onset of cognitive decline secondary to HIV infection. This has been seen in large observational studies (Portegies 1993) and in post hoc analyses of studies looking at the impact of early use of AZT on the overall natural history of HIV disease where HACM was one considered endpoint. In one post hoc review of three placebo-controlled trials (ACTGO19, VA298, and Concord) that compared AZT in asymptomatic and early symptomatic HIV infection to placebo, the incidence of dementia due to HIV disease was 3.1% in the early-treatment group as compared with 6.1% in the late-treatment group, suggesting that early intervention with AZT, even in lower doses (that is, 300 to 600 mg/day), may be beneficial for halting the progression of HACM (Baldeweg 1995).

Recent research in the treatment of systemic HIV disease has demonstrated the benefits of combination antiretroviral therapy (that is, as a minimum treatment, two nucleoside reverse transcriptase inhibitors such as AZT and 3TC with or without a protease inhibitor and/or a nonnucleoside reverse transcriptase inhibitor) over AZT monotherapy. Theoretically, a combination of agents may be necessary to treat HACM effectively, because AZT monotherapy has been shown to be limited in its sustained clinical effect. Emerging treatment goals for HACM focus on achieving therapeutic levels in the CSF by using a combination of antiretrovirals to halt the progression of cognitive decline. Many of the current agents do not effectively penetrate the blood brain barrier, but novel antiretroviral agents that do are currently under investigation.

Researchers are also investigating neuroprotective agents, which are designed to stop the process of neuronal dysfunction set in motion by the presence of HIV in the brain. Cytokine-modulating agents are also under investigation because theoretical evidence suggests that cytokines liberated in response to the presence of HIV in the brain may be related to HACM. Both classes of these agents attempt to alter the pathophysiological process driven by the immune system’s attempt to fight HIV in the brain. They may be effective in treating HACM in the future. In developing treatment plans, psychiatrists should take into account any coexisting disorders, such as depression and substance use, which may affect cognitive function. While this treatment is essentially symptom management and does not alter the underlying pathophysiological mechanism driving HACM, it may have substantial benefit to the patient’s condition.

Can anything be done for the fatigue and apathy?

Fatigue, apathy, anergia, amotivation, and dysphoria are particularly troublesome symptoms that have a significant impact on a person’s quality of life. Even in the absence of major depression, people living with HACM and late-stage HIV disease may experience these symptoms.

Low-dose psychostimulants can be used to treat these symptoms. Methylphenidate or dextroamphetamine may be started at 5 mg each morning and titrated upwards in 5 mg increments every 48 hours to a daily maximum of 40 mg twice daily. Mean dosage is usually between 10 and 20 mg, and some patients benefit from a booster dose at noon to carry the effect of the morning dose through the afternoon. Doses after 13:00 should be avoided because they may interfere with nighttime sleep. Patients should be told that stimulants can be addictive, and physicians should prescribe them judiciously to mitigate any possible abuse or misuse. This concern, however, should not prevent psychiatrists from prescribing psychostimulants when appropriate. Physicians should also be aware that, although stimulants have been demonstrated to be effective in open-label trials and are considered effective clinically, they have not been evaluated in randomized, double-blind, placebo-controlled studies, and HACM is not an approved indication for their use.

EPILOGUE

Ravi wanted his HACM managed aggressively. After baseline neuropsychological testing, his AZT dose was increased to 800 mg/day. He tried to increase to 1200 mg/day but was unable to tolerate the side effects. Follow-up neuropsychological assessment was planned for...
six-month intervals to see if objective evidence of improvement in neuropsychological function could be documented in order to help guide treatment decisions, particularly decisions about the aggressiveness of antiretroviral dosing.

The psychiatrist also offered Ravi a therapeutic trial of antidepressants to treat the depression. He advised Ravi to decrease his alcohol intake and prescribed a short-acting benzodiazepine to replace the over-the-counter hypnotic Ravi was using to manage his sleep problems. They also discussed a trial of low-dose trazadone (50 mg at bedtime) as a hypnotic alternative to benzodiazepines. The psychiatrist and Ravi discussed discontinuing ddI and switching to 3TC as an antiviral alternative that may cause less sleep disturbance, and Ravi agreed to add a protease inhibitor to his regimen.

**CASE STUDY**

**DEMENTIA WITH BEHAVIOURAL COMPLICATIONS**

Carlo is a 37-year-old gay man with AIDS and a CD4 lymphocyte count of 10. Until four months before he was assessed, he was in his usual state of health. At that time, he began to complain of an increase in memory difficulties and inattention. This was followed by a steady decrease in cognitive capacities and an increase in intrusive, argumentative, impulsive, and bizarre behaviour.

When he was examined, he had no insight into the inappropriateness of his behaviour and was highly concrete in his interpretation of his situation. He reported that he had stopped his antiretroviral medications four months ago because he felt he had been cured of HIV disease. He was emotionally labile and, at times, argumentative but denied having a sense of euphoria or grandiosity.

He was fully oriented in all spheres and scored 25/30 on a Folstein MMSE, with deficits in serial sevens and sequential task performance. He was unable to perform Luria hand sequence manoeuvres, was markedly inaccurate and concrete in his clock drawing, and was unable to perform complex tasks requiring planning, organizing, and sequencing.

He had no history of personal or family psychiatric problems. He denied alcohol and drug use and had no new medical conditions or medications. He displayed no focal findings other than cognitive, behavioural, and personality changes, suggesting a frontal lobe syndrome.

An occupational therapy assessment confirmed that he was unable to perform basic activities of self-care required for independent living, and a home visit revealed that his apartment had become unsafe. MRI revealed patchy T2-weighted white matter lesions in the frontal region with diffuse cortical and central atrophy and enlarged ventricles. Two sleep-deprived electroencephalograms showed diffuse slow-wave activity but no focal discharges.

Carlo appeared to have an organic mental condition secondary to HIV disease. Given how rapidly the condition progressed, the differential
Cognitive Disorders in People Living with HIV Disease

Diagnosis included severe HACM (MSK stage 3) and PML.

Carlo did not have the capacity to make treatment decisions and, because of his behaviour, was found to be at risk of imminent harm to himself and others: he was admitted involuntarily under provincial mental health legislation.

What impact does HACM have on behaviour?

HACM appears to make people vulnerable to affective and behavioural disorders that may lead them to seek psychiatric care. Psychiatrists may need to treat both the behavioural symptoms and, in collaboration with the treating physician, the underlying HACM. It is important to remember that patients with HACM are vulnerable to the side effects of most medications, in particular to the antipsychotic agents that block dopamine (D2) receptors. As Hriso and others (1991) note, psychiatrists should use lower doses of these agents to treat delirium and behavioural disorders in people living with HIV, doses comparable to those used with geriatric patients.

Strategies to manage behavioural complications include pharmacologic agents as well as environmental manipulations to enhance function and safety.

In the early stages of HACM, people can often adjust to their cognitive losses and continue to function normally. They can use an adaptation and compensation strategy to reinforce their remaining cognitive abilities and to compensate for their limitations. As HACM progresses, cognitive problems become more marked, and people with HACM have more difficulty adapting to them. At that stage, caregivers can collaborate to develop an environmental engineering approach which works to structure the environment to minimize the impact of these limitations. People with HACM and their caregivers must be educated to use these strategies effectively.

Adaptation and Compensation Model

To help them manage their lives, psychiatrists can advise people with HACM to:

- keep a written record of appointments and important dates
- slow down and undertake only one task at a time
- keep mentally active (for example, play games such as Scrabble, cards, and video games and do crosswords and jigsaw puzzles—ensuring that the activities are challenging but not frustrating)
- get plenty of rest
- schedule appointments midday (because cognitive problems are exacerbated by fatigue)
- improve their ability to concentrate and focus by problem solving out loud
- avoid stressful situations and environments such as busy shopping malls
- use stress reduction and relaxation techniques
- avoid tasks they once did easily but now find frustrating (for example, balancing a cheque book)
- exercise regularly
- use an automated pill box to manage their own medications as long as possible

By actively encouraging and supporting people’s efforts to manage their cognitive problems, psychiatrists can also help improve their emotional state.

Environmental Engineering

With environmental engineering, psychiatrists can help caregivers provide an external structure that may make the world less confusing for someone with HACM. The more structured the environment, the easier it is for people to understand and process what is happening around them. This includes:

- frequently orienting the person to the year, month, date, time, and place
- keeping calendars and clocks in view (people often find digital clocks easier to read)
- posting the day’s date and the person’s schedule for the day on a wall or blackboard
- using nightlights, particularly for people who become disoriented in the dark
- ensuring that familiar objects and pictures are placed in the person’s room (especially if the person is in a hospital or other setting away from home)
- keeping furniture, personal objects, and daily living utensils in the same place
- having the same home-care attendant assigned to the patient
- putting up large, clear signs to label different rooms
- ensuring the person carries an identification card with the names, addresses, and phone numbers of caregivers on it
presenting information slowly, one step at a time, and asking the person to repeat instructions to make sure they are understood
encouraging the person to talk about familiar places, interests, and past experiences
assessing the person’s ability to manage stimulation and adjusting the amount of stimulation in the environment accordingly (for example, keeping the space uncluttered, setting a maximum number of people to visit at one time)
removing anything from the environment that seems to trigger anxiety
simplifying tasks and allowing the person to do them at his or her own pace.

EPILOGUE

The psychiatrist sought a substitute decision maker for Carlo and recommended antiretroviral treatment (AZT, 3TC, and indinavir) to try to slow the process of HACM as well as low-dose antipsychotic medication for behaviour control. Carlo developed significant extrapyramidal symptoms on oral haloperidol 1 mg at bedtime and was switched to oral risperidone 1 mg twice daily with minimal benefit. A low-dose anticonvulsant was added when behaviour was inadequately controlled with antipsychotics alone. Carlo settled with a combination of risperidone 2 mg twice daily and divalproex sodium 500 mg at bedtime.

In this case, Carlo’s HACM was too advanced to be amenable to the adaptation and compensation model. Wandering remained a significant problem. Ultimately, Carlo accepted a transfer to a secure chronic nursing care facility. His cognition continued to deteriorate, and he died one month after transfer to the chronic care facility.

CASE STUDY

DELIRIUM

Louise is a 37-year-old, HIV-seropositive woman with a three-day history of confusion and disorientation. Concerned that Louise was hallucinating, her roommate brought her to the hospital emergency room and reported that Louise had been fairly well until five days earlier, when she began to be short of breath walking up stairs. The confusion and disorientation developed shortly after.

Over the past six months, Louise had occasionally been forgetful. She had made greater use of stick-on notes and reminder cues, but she had no overt functional limitations. For the past few days, however, she had been sleeping poorly, was difficult to rouse during the day, and was, at times, unsure of her whereabouts. At other times, she seemed less confused. Louise had been afraid to sleep at night because she saw things moving in the dark and was frightened that people were waiting to attack her.

She had not had a CD4 lymphocyte count done in the past two years and was on no medications. She had no complications due to HIV disease and no other major medical conditions, but she had a history of polysubstance dependence, including injection drugs and alcohol. Louise had been off all substances for three years and, until she fell ill one...
week ago, had maintained strong contact with her 12-step group. She prefers to ignore the impact of HIV on her life and does not like to see health care workers.

When Louise was examined, she looked ill and was in some respiratory distress. She was not oriented to date or place, though she was oriented to person. She was unclear about how she came to the hospital, appeared highly distractible, was unable to register four words adequately, and displayed poor recall. She could not cooperate with serial sevens examination or Luria hand sequence manoeuvres. She was somewhat suspicious and kept checking behind the curtain, certain that someone was there. At times Louise was combative, unwilling to accept care; on two occasions she pulled out her intravenous line. Laboratory investigations indicated that she was anemic and hypoxic. The drug screen was negative.

What are the signs, symptoms, and course of delirium?

Delirium is the most frequent neuropsychiatric complication in hospitalized patients living with AIDS. The etiology is often multifactorial. Although delirium may occur in patients with no or minimal previous neurocognitive impairment, it is most often caused by an organic insult to a brain rendered vulnerable by HIV infection.

Louise displayed classic symptoms of delirium, characterized by a disturbance in consciousness with reduced ability to focus, sustain, or shift attention, with accompanying disturbances of cognition and perception. Delirium generally develops rapidly over a short period of time and follows a fluctuating course over the day.

What is the recommended management for delirium?

The primary goal in managing delirium is to identify and treat the underlying factors. In Louise’s situation, her delirium was related to an underlying systemic infection, PCP. Recommended management, besides treatment of pneumonia, includes treating the symptoms of delirium, including the confusion, perceptual abnormalities, and agitation, so that the patient is better able to cooperate with interventions necessary for treating the underlying medical disorder.

Recommended treatment includes antipsychotic medication in low doses to help resolve confusion and calm the patient, although caution must be used in dosing because patients living with HIV disease frequently develop extrapyramidal side effects when high-potency antipsychotics such as haloperidol are used. Practitioners should identify target symptoms (for example, agitation, sleep disturbance, confusion, and dangerous behaviour), note the effect of the antipsychotic on those symptoms, and prescribe the minimum dose necessary to control them. Most patients will respond to a daily dose of haloperidol of 0.5 to 5.0 mg, but higher doses may be necessary. According to Breitbart and others (1996), lorazepam, a short-acting benzodiazepine, is useful in augmenting the effectiveness of antipsychotics in treating delirium, particularly in achieving sedation, but is not effective as a sole agent to manage delirium. Given the morbidity and mortality associated with untreated delirium, every effort should be made to use antipsychotics effectively to manage symptoms.

When untreated delirium threatens the safety of the patient or the treatment team, mechanical restraint may be used to make the situation safe and allow the patient to be medically stabilized. When those objectives have been met, the restraints should be removed.

Delirium is frightening to the patient and to family and friends. Every effort should be made to reassure and reorient the patient by explaining the procedures and establishing a calm environment.

EPILOGUE

Louise was treated with 0.5 mg intravenous haloperidol. After 30 minutes, the symptoms of agitation and confusion were reassessed. She remained somewhat combative and confused, so a second haloperidol dose of 1.0 mg was given. After another 30 minutes, she remained agitated and was given an additional 2.0 mg of haloperidol with 1.0 mg of lorazepam to help with sedation, which led to significant calming. She continued to be given a daily dose of haloperidol 2.0 mg at bedtime over the next three days until her confusion completely resolved (as a result of the treatment for the pneumonia), at which time haloperidol was discontinued.
CONCLUSION

As treatments for the management of opportunistic conditions secondary to immunosuppression improve and combination therapies give greater hope for the management of systemic HIV disease, the neuropsychiatric, cognitive, and neurologic consequences of HIV infection become increasingly important. Therapies that can effectively cross the blood brain barrier and halt the progression of cognitive decline secondary to HIV infection will become more necessary.

Psychiatrists, neurologists, and primary care HIV physicians must be able to identify HACM in its earliest stages and to monitor patients’ cognitive deficits and their response to treatment. Psychiatrists, in particular, will be called upon to differentiate dementia from depression and substance-related disorders and to treat the affective and behavioural manifestations associated with HACM. To address their patients’ needs adequately, psychiatrists will need an empathic biopsychosocial appreciation of the complex interacting factors involved in cognitive disorders.

RESOURCES


MULTIPLE-CHOICE QUESTIONS

1. Which one of the following statements about HACM is true?
   a) Pharmacologic management of HACM should include antiretroviral combination therapy.
   b) The majority of patients with cognitive impairment due to HIV-1 follow a rapidly progressive deteriorating course.
   c) The lifetime prevalence of MCMD in HIV-1–infected individuals is approximately 80%.
   d) Cognitive deficits associated with HACM cannot be reliably distinguished from major depression in an HIV-infected individual.
   e) HACM is caused by a CMV infection.

2. Which one of the following statements about HACM is false?
   a) The lifetime prevalence of HACM MSK ≥ 2 (HADC) in HIV-1–infected individuals is approximately 15% to 19%.
   b) The lifetime prevalence of MCMD (MSK stage 0.5 or 1.0) in HIV-1–infected individuals is approximately 40% to 60%.
   c) HACM MSK Stage ≥ 2 (HADC) is the index AIDS-defining diagnosis in approximately 4% of HIV-1–infected individuals.
   d) No single diagnostic test taken alone can make the diagnosis of HACM; rather, diagnosis is made by considering data from history and investigations taken together.
   e) No specific risk factors have been correlated with HACM.

3. Which one of the following statements about HACM is false?
   a) The Folstein MMSE is not a sensitive screening tool for HACM.
   b) Development of novel antiretrovirals that adequately penetrate the blood brain barrier is an important next step in the pharmacologic management of HACM.
   c) The human immunodeficiency virus enters the brain once the immune system is significantly weakened.
   d) Methylphenidate has been shown in open-label trials to be effective in treating apathy, fatigue, and concentration difficulties associated with HACM.
   e) Lorazepam and haloperidol have a role to play in the management of delirium in HIV-1–infected patients.

4. Which one of the following statements is true?
   a) HACM frequently results in focal neurologic findings like right-sided hemiparesis or localized sensory losses.
   b) Patients with HADC should be encouraged to undertake complex tasks to keep their minds sharp even if the activity is frustrating to them.
   c) HADC is characterized by agnosia and dense aphasia.
   d) HACM is a complex of neuropsychiatric symptoms characterized by a slowing-down process in the domains of affect, behaviour, cognition, and motor function.
   e) The most common behavioural change associated with HACM is disinhibition.

Answers on page 151