

FOCUS A GUIDE TO AIDS RESEARCH

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AIDS Dementia Complex: Diagnosis and Management

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Since the first AIDS cases were described in 1981, a variety of groups around the world have confirmed that people with AIDS and ARC can develop neurological problems as a consequence of infection with the Human Immunodeficiency Virus (HIV) and that the onset of these complaints may be the first sign of disease progression.

Recognizing this clinical consensus, the Centers for Disease Control (CDC) amended, in August 1987, the surveillance definition of AIDS to include the AIDS Dementia Complex (ADC), the deterioration of mental capacities caused by direct infection of the brain by HIV.

Because ADC is one of the most insidious forms of neurological dysfunction that affects people with AIDS, and is increasingly reported among people with HIV infection, clinicians need to know how it can be recognized and managed.

Mechanism of HIV Infection of the Brain

In early 1985, autopsy findings reported the presence of HIV in the brains of patients who had demonstrated significant confusion, disorientation and memory loss prior to death, and gave support to the hypothesis that HIV itself was in some way responsible for these changes.

A series of additional findings confirmed this view. It was shown that HIV could be introduced into the peripheral veins of chimpanzees and later could be detected in their brains. This strongly suggested that HIV could travel through the blood stream, cross the blood-brain barrier and survive within the brain itself.

It was reported that the HIV virus was very similar in structure to another retrovirus, the visna virus, which had long been known to cause a degenerative neurologic disease in sheep. HIV has since been included in this group of viruses — the lenti- or "slow" viruses — which, after a lengthy period of infection, cause neurologic disease in a variety of animal hosts including primates, goats, horses, and mice.

Further, HIV has been isolated in the cerebrospinal fluid, brain, spinal cord, and peripheral nerve(s) of patients with HIV-related neurological disorders. In addition, several autopsy studies have shown significant abnormalities in the brains of 70 to 90 percent of patients who had died of AIDS whether or not the individuals had displayed clinical evidence of brain disease.

Finally, a variety of cell types found in the central nervous system were shown to be capable of infection by HIV and since then these infected cells have been harvested from the brains of

patients with AIDS. Most significantly, the macrophage, a white blood cell that is one of the first cells to be infected by HIV, has also been shown to be a site of viral reproduction in the brain. It is thought by many that the virus crosses the blood-brain barrier using the macrophage as a "Trojan Horse."

AIDS Dementia Complex

It is important to understand that ADC is a clinical diagnosis that includes cognitive, behavioral and motor components. Early cognitive symptoms include difficulties with concentration and memory, a general slowing of mental functioning and, often, personality changes. The successful completion of daily tasks may become difficult for people with ADC. Friends or family members may report the patient "is not himself," or "isn't as quick or as witty as he used to be." Common behavioral symptoms include social withdrawal and apathy; occasionally, agitated and psychotic behavior may also appear. Early motor problems can include difficulty with balance, clumsiness and leg weakness.

ADC is a clinical diagnosis that includes cognitive, behavioral and motor components. Practitioners must be sensitive to the interplay among these.

The exact epidemiology and natural history of ADC has not been well defined. Seen most often in those with an AIDS diagnosis, ADC has been reported in a small number of HIV-positive men who were otherwise healthy and in whom the development of these symptoms predated the development of any opportunistic disease. Once clinically apparent symptoms of ADC emerge, a progressive decline in function can be expected. The precise time course, however, is uncertain and some patients have experienced at least temporary improvement in their symptoms.

The late stages of ADC include: global dementia, often with little or no ability or willingness to speak; multiple neurologic abnormalities, including bowel and bladder incontinence; and an overall vegetative state requiring total bed care. Consciousness is usually preserved, although the patient may lie in bed, stare vacantly and have little social involvement with his or her caretakers.

While the extent and degree of ADC remains unclear, researchers estimate that early in the course of AIDS, approximately one-third of patients will develop moderate to severe dementia and one-quarter will have mild dementia that can be documented only by careful neuropsychological assessment. As infection progresses, as many as two-thirds of AIDS patients may develop some signs of dementia, though these signs may not always be clinically apparent. Estimates like these need to be confirmed by systematic, longitudinal studies.

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Finally, while there is currently no treatment for dementia, AZT has been shown to produce at least temporary improvement in ADC symptoms in some patients. (See "Recent Reports" below for further information.)

Clinical Assessment of ADC

When asked to assess HIV-infected patients, mental health practitioners need to remember that changes in mental functioning can occur for a variety of reasons. Some of these arise from treatable opportunistic infections, such as toxoplasmosis or cryptococcal meningitis, or from other treatable disorders such as nutritional deficiencies, metabolic disorders, psychiatric disorders such as depression, recreational drug use, and the side effects of medication.

ADC is a diagnosis of exclusion that requires the practitioner's discretion. The diagnostic criteria used by the CDC include a positive antibody test for HIV; a negative lumbar puncture; and a negative CT (Computerized Tomography) or MRI (Magnetic Resonance Imaging) scan, or findings consistent with atrophy. In addition, they require "Clinical findings of disabling cognitive and/or motor dysfunction interfering with occupation or activities of daily living, or [in children] loss of behavioral developmental milestones . . . progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings."

In working with people with AIDS, the mental health practitioner must be aware of the early symptoms of cognitive decline that have been outlined above. This is especially important because some of the opportunistic infections, which can cause altered mental states, can be successfully treated. When such symptoms appear, especially in conjunction with complaints of headache, stiff neck or fever, a patient should be immediately referred to his or her physician for evaluation.

During clinical evaluation of ADC, special attention should be given to performing a thorough mental status exam including assessments of orientation, attention, memory, language abilities, and judgment. It is important to keep in mind, however, that the brief screening exams in common use (for example the Folstein Mini Mental Status Exam) often fail to detect early and subtle deficits associated with ADC.

With the patient's permission, it is helpful to interview family members and friends about their observations of the patient. This is particularly important since individuals with ADC may be unaware of the extent of their problems and may underreport symptoms. Documentation of these changes on initial and follow-up visits is essential.

Neuropsychological Assessment of ADC

The individual suspected of having neurological complications related to AIDS should always receive a complete medical and neuropsychiatric evaluation. This should include a neurological exam, neuroradiological procedures and neuropsychological testing.

As diagnostic tools, neuropsychological tests have distinct advantages over traditional clinical interviews or mental status exams. The neuropsychological battery is standardized and integrated with a normative data base. Cognitive abilities and behavioral presentation can be quantified in a manner that allows for an initial clarification of a patient's present condition and for accurate retest comparisons, and helps in the planning of patient care.

The neuropsychological battery should include measures of fine motor speed, verbal fluency and language comprehension, attention and concentration, memory, problem-solving skills, and visual-spatial constructional skills. Measures of mood state and psychiatric symptoms should also be included.

Formal neuropsychological testing requires one to four hours. People with AIDS may fatigue easily and may not have the stamina for extensive testing, therefore a brief and focused testing approach may be necessary. Neuropsychological evaluation may not be practical in some settings because an experienced neuropsychologist may not be available.

Differentiation from Depression

Mental health professionals often must differentiate the early symptoms of ADC from functional depression. This can be a difficult task and usually formal neuropsychological testing is required.

Several clinical points, however, may be helpful. First, apathy is not depression. Patients who are apathetic may be lethargic and indifferent, but they usually do not reach out emotionally or communicate affective pain. The interviewer is encouraged to pay attention to how he or she feels while interviewing the patient. Depressed patients usually leave the interviewer feeling sad and distressed, while apathetic dementing patients leave the interviewer feeling emotionally flat. Again, if it is possible, the interviewer should try to verify impressions with the patient's friends or family members. Be aware also that a patient who is depressed is more likely to consider suicide than the patient who is dementing.

Second, take a psychiatric history. Patients with a history of affective disease are much more likely to have a recurrence of major depression than those without such a history, even in the face of a life-threatening illness. Also, patients with a family history of depression are at greater risk of becoming functionally depressed.

Third, the passage of time will be helpful in verifying conclusions. If cognitive problems progress, a diagnosis of ADC becomes more likely.

Finally, keep in mind that dementia and depression can and do often coexist. If the usual signs and symptoms of depression are evident, the patient should be referred for psychiatric evaluation and may deserve a trial of anti-depressants.

Management of the Patient with ADC

As ADC progresses, a patient's ability to participate in the management of his or her disease is impaired. In the early stage of ADC, however, the patient can and should actively participate.

During this period, educating the patient and caregivers about mental and physical changes that may occur is helpful. Including the patient in decision-making, openly discussing these issues with caregivers, and having the patient set realistic goals helps the patient maintain a sense of responsibility and self esteem. Therapists should also be aware that patients and their families may misunderstand the term "dementia," which has a distorted connotation in our culture. Be sensitive to this and focus instead on the concepts of the patient's changing abilities to feel, react and think.

Because depression and anxiety frequently co-exist with ADC, it is important that patients be offered psychotherapy, support groups and, if indicated, a trial of anti-depressant medication.

In the second stage of ADC, patients lose their abilities to monitor, control and change troublesome behaviors, and to adapt to changes in the environment. Caregivers need to intervene and provide external structure to help make the world seem less confusing and more predictable. Environmental engineering minimizes the impact of the patient's lost abilities. (See "Recent Reports" below for information on a brochure about caregiver strategies.)

Attention should be paid to orienting the patient to time and date, structuring environment and routine, communicating in ways the patient can understand, and regulating the amount of sensory stimulation the patient receives.

In general, use strategies that will avoid confusing the patient. Environment and routine should be kept consistent and familiar. Keep in mind that long-term remote memory is usually intact in individuals with ADC, while memory for recent events is

impaired. Present information slowly and one step at a time. Remember that too much or too little sensory stimulation may increase confusion, agitation and fear.

Finally, mental health practitioners should make regular assessments of the patient's ability to live independently and should be ready to refer patients for legal advice, home health care or psychiatric hospitalization.

The practitioner also needs to continue to educate family and friends about the patient's condition and provide needed emotional support. It is particularly important for significant others to understand that a patient's behavior is not willful or deliberately difficult.

Conclusion

People with AIDS are at significant risk of developing cognitive impairment and the mental health practitioner working in this area must become familiar with the symptoms of the AIDS Dementia Complex. Developing a referral relationship with an AIDS-knowledgeable psychiatrist and neuropsychologist will help to allay a practitioner's concerns and improve care of patients with this disorder.

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Diagnosis/Treatment/Prevention

Common CNS Disorders Caused by AIDS—Related Diseases

James W. Dilley, MD

People with AIDS may develop one or more of a variety of central nervous system (CNS) disorders, some of which can cause changes in mental status similar to those seen in the AIDS Dementia Complex. This brief review will cover the most common of these disorders, with particular attention paid to those affecting the brain, their clinical presentations, and the role of HIV in their development.

Opportunistic Infections and Neoplasms

The most common of the neurological disorders found among people with AIDS are Cryptococcal meningitis and Toxoplasmosis. A review of data from the Centers for Disease Control (CDC) reveals that of the first 23,307 patients with AIDS reported to the CDC, 5.4 percent, or 1,252, were diagnosed with Cryptococcal meningitis and 2.68 percent, or 625, were diagnosed with *Toxoplasma gondii* encephalitis.

Less frequently observed were two cancerous conditions affecting the brain, Progressive Multifocal Leukoencephalopathy (PML) and Primary CNS Lymphoma. These conditions were reported at a rate of .8 percent and .74 percent respectively. The total percentage of AIDS patients who present with primary neurological disease is 9.6 percent. Many people with AIDS, who do not present with a primary neurological disease, eventually develop one in the course of their infection with HIV.

Cryptococcosis

Cryptococcosis is ubiquitous in nature and is the most common fungus to infect the central nervous system. It is found frequently in soil, is particularly prevalent in areas inhabited by

pigeons, and is believed to be contracted by the inhalation of aerosolized droplets. Lung infections are rare, but can also be caused by this organism in patients who are immune suppressed. No person-to-person transmission of this disease has ever been reported.

Among those with AIDS, cryptococcal disease is found most often in I.V. drug users and in Haitians who are not I.V. drug users. While cryptococcal disease can occur in many organ systems in the body, it most frequently causes an inflammation of the meninges, the covering of the brain and spinal cord. Cryptococcal meningitis usually develops slowly over weeks or months and is characterized by fever, headache and malaise. Stiffness of the neck and an aversion to sunlight occur in about a third of patients while mental status changes have also been reported in 20 percent of patients and may be the only presenting complaint.

Diagnosis is made by analysis of cerebrospinal fluid obtained by lumbar puncture. Between 50 and 75 percent of patients will respond to anti-fungal treatment. Indefinite weekly treatment is recommended after the acute illness is controlled since the incidence of relapse is high.

Toxoplasmosis

Toxoplasma gondii is an intracellular parasite that is found in all human populations. Regional differences occur, however, and antibodies are found in 40 to 50 percent of healthy young American adults compared to 90 percent of healthy adults in developing countries.

The parasite is commonly carried by cats and it is thought that it is most often transmitted to humans through an oral-fecal route. Additionally, the organism can be found in beef, lamb and pork, and can infect humans who have eaten undercooked, infected meat. Epidemiologically, toxoplasmosis in AIDS patients in the United States is seen approximately 12 times more often in those patients from Haiti than in all other risk groups combined. There is also a higher incidence among Hispanics from the Caribbean basin than in those from the United States.

Once acquired, infection is for life. An intact immune system keeps the organism at bay and it is the progressive immune destruction, characteristic of AIDS, that allows previously-acquired infections to grow into clinical disease. Because there are few new toxoplasma infections among people with AIDS, such individuals should feel free to keep their cats. However they should use caution when emptying the litter, and should wash hands thoroughly after contact with cat or litter.

Clinical manifestations of toxoplasmosis are varied, and usually occur slowly over a period of weeks. Symptoms include a period of malaise, fever, headaches and seizures. The most common presentation includes some focal neurologic symptom, such as a specific muscle weakness, or the presence of abnormal findings on a neurological exam. Mental status changes, including confusion and disorientation are also common.

Diagnosis is most often made by CT (Computerized Tomography) or MRI (Magnetic Resonance Imaging) scan. These radiographic procedures show characteristic multiple ring-enhancing lesions throughout the brain. MRI is more sensitive than CT in demonstrating these abnormalities. Diagnosis may also be established either by initiating treatment and monitoring improvement, or by brain biopsy. Approximately three-fourths of patients will respond to treatment and, as with cryptococcal disease in patients with AIDS, ongoing, even lifelong, therapy is required to forestall relapse.

Progressive Multifocal Leukoencephalopathy (PML)

PML is a slowly progressive viral disease that causes destruction of myelin, the "insulating" wrapping that covers nerves and promotes the transmission of impulses throughout the nervous system.

PML is most often seen in patients with certain cancerous

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Common CNS Disorders . . .

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conditions of the blood, or conditions in which a patient's cell-mediated immunity is impaired.

The onset of PML in people with AIDS is gradual. Focal neurologic signs are common, including impairment of vision and speech, mental deterioration, sensory abnormalities, and ataxia (unsteady, wide-based gait). Unlike the other disorders discussed, headaches are uncommon and the patient rarely has fever. Diagnosis is made on clinical symptoms and CT or MRI findings. Definitive diagnosis is made only on biopsy but this is rarely necessary since no treatment is presently available. Death usually occurs within one year.

Primary CNS Lymphoma

These rare tumors affect the brain and are most common in patients who are immunosuppressed. Their underlying pathology is not well understood. Symptoms include disordered consciousness or cognition, hemiparesis (weakness in half the body), headaches, seizures and incontinence. Diagnosis is made on CT scan, although the appearance of the tumors can be confused with toxoplasmosis lesions. Definite diagnosis is made only by brain biopsy. Radiation therapy is the only treatment available, however, response to treatment is poor and average survival is about two months.

Conclusion

People with HIV infection may be the focus of a variety of neurological diseases. Armed with information about the diagnosis and symptoms of these, the mental health practitioner is better prepared to work with this group of patients.

James W. Dilley, MD, is the Project Director of the AIDS Health Project in San Francisco.

BRIEFS

Recent Reports

AZT Potentially Effective in Diminishing Neurological Diseases. The results of a study of seven patients suffering from a variety of AIDS-related neurological diseases show that AZT may in part reverse the neurological dysfunction that can occur with HIV infection. The study's authors stated that the results form the basis for a larger study.

Researchers from the National Institutes of Health studied three patients with AIDS dementia, two with peripheral neuropathy, one with both neuropathy and dementia, and one with weakness in the lower extremities. They reported in the *Annals of Neurology*, Supplement to Volume 23, 1988, improvement in six of the study's patients, three of whom sustained improvement for five to 18 months.

Evaluation of patients included routine general and neurological examinations, CT and PET scans, lumbar puncture, and tests of attention, memory, coordination and nerve conduction. The four patients with dementia, who had suffered from a significant decline in intellectual functioning, improved on tests of attention, fine-motor coordination and memory

within two to eight weeks of treatment with AZT.

The three subjects with peripheral neuropathy, including one who also had dementia, all showed improvement after treatment with AZT. Weakness and sensory abnormalities in the extremities, motor strength, and amplitude and velocity in nerve conduction all improved. The patient with profound lower-extremity weakness, who was on AZT for only three weeks because of severe Kaposi's sarcoma and lower limb edema, showed little neurological improvement, and was one of two patients who died during the study period.

The authors stressed that HIV-infected patients may develop a number of neurological syndromes — dementia, peripheral neuropathies, polymyositis and myelopathy — and that these may be the predominant clinical manifestations of HIV infection. While some of these may spontaneously improve, others, like AIDS dementia, rarely resolve in the absence of treatment.

The authors acknowledged the small size of their study sample and problems among their subjects with AZT toxicity. They also stated that the four patients with dementia, who responded well to AZT, were treated relatively early in the course of their neurological dysfunction, while the two patients who responded minimally to the AZT were treated for more advanced neurological syndromes.

(Editor's note: Further studies of AZT in the treatment of the AIDS Dementia Complex are currently underway at various AIDS Treatment and Evaluation Units around the country.)

AIDS' Effects on the Brain is an AIDS Health Project brochure that offers concise and comprehensive pointers for non-professionals on the warning signs of ADC and on helping the patient to manage this disorder once it is diagnosed.

Since there is currently no cure for ADC, patients must rely on caregivers to provide an environment that enables them to respond to this disability. The brochure, which is available in English and Spanish, discusses management of the patient's environment in five areas: orientation, structure, communication, stimulation and safety.

AIDS' Effects on the Brain is available from the AIDS Health Project, Box 0884, San Francisco, CA 94143-0884, at a price of 65 cents per copy for 1 to 25 copies and 40 cents a copy for 26 or more copies.

Next Month

The severity of AIDS and the media exposure it has received has created a population that copes in a variety of ways to the threat of exposure. In the August issue of **FOCUS**, **Charles R. Tartaglia, MD**, and **C. Richard Filson, EdD**, will discuss the AIDS-conscious patient, the individual who seeks evaluation, treatment and emotional solace from his or her physician and who is eventually referred to a mental health professional for counseling.

In addition, **Francisco Fernandez** will explore the use of psychostimulants in the treatment of psychological disturbances, such as HIV-related depression and ADC. He will discuss the historical bias in the U.S. against the use of drugs to treat psychological symptoms, and the benefits and problems of pharmacological alternatives.

FOCUS A GUIDE TO AIDS RESEARCH

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The amount of research information now appearing in the medical and lay press staggers most AIDS health care and service providers. The goal of **FOCUS** is to place the data and medical reports in a context that is meaningful and useful to its readers.

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