# The Neurological and Electroencephalographic Changes in AIDS

**Peter G. Bernad**

"Medical insight and medical help — this is the conclusion — are the way to the courage to be; the medical profession is the only healing profession." This was quoted from Paul Tillich in *The Courage To Be,* 1952. Sir William Osler over 100 years ago suggested to his students that if one knew syphilis then one actually had knowledge of all medical science. A similar statement could be made about HIV (Human Immunodeficiency Virus) disease or AIDS (Acquired Immunodeficiency Disease Syndrome). The purpose of this presentation is to outline in a brief manner the neurological and specifically the electroencephalographic manifestations of HIV infection.

Following a marked decrease in cell mediated immunity, there is a selective decrease in the TI lymphocyte population, both in terms of number as well as in terms of function. As the T Helper/Inducer subset is lessened the Suppressor/Cytotoxic subset is activated. Patients are devastated by multiple opportunistic infections and neoplasms as well as other neurological complications of AIDS.

Many infections cause disease in the central nervous system.[1] These include viral infections such as papovavirus, human B19 Parvovirus infection and cytomegalovirus (and nonviral infections such as aseptic meningitis). Patients with HIV disease may present with aseptic meningitis. Various bacterial infections are also seen. Nonviral and nonbacterial infections include Protozoa such as Toxoplasma gondii. Fungal infections include Cryptococcus neoformans, Aspergillus fumigatus and Candida albicans. Other infections are mycobacterial infection. This includes Mycobacterium tuberculosis and Mycobacterium avium-intracellulare, which is also referred to as atypical mycobacterial infection.

HIV and more specifically Human Immunodeficiency Virus - type I (HIV-I) is an example of neurotropic virus. Neurons, macrophages, specific lymphocytes, and certain colorectal cells have special protein receptors called CD4 receptors.[2–6] These special receptors on these particular cell surfaces must be present for HIV-I to occur. The central nervous system may be affected by a primary central nervous system lymphoma, or by secondary involvement of the central nervous system from systemic lymphoma, plasma cytoma, or Kaposi's sarcoma.

In AIDS certain cranial nerve syndromes are seen that include chronic inflammatory polyneuropathy, and Bell's palsy. Peripheral nerve syndromes are also seen such as chronic inflammatory polyneuropathy, distal symmetric neuropathy, and frequently herpes zoster radiculitis.[1]

Vascular disease may also affect the central nervous system in patients with AIDS. Thrombocytopenia in patients with HIV-I predisposes these patients to cerebral hemorrhage, and various types of anemia as seen in association with AIDS may also predispose the nervous system to dysfunction. Non-bacterial thrombotic endocarditis results in cerebral infarction. Central nervous system lesions secondary to arteritis are also seen as well as central nervous system lesions secondary to bacterial endocarditis.

Reduced visual acuity is common during HIV infections. It may be caused by the virus itself (AIDS-related retina microangiopathy) or by opportunistic infections.[7,8]

## NEUROLOGICAL MANIFESTATIONS OF AIDS

The very first cases of AIDS were recognized but were not named or identified as such, probably in the early 1970s. These anecdotal reports of unusual cases usually ended up in clinical pathological conferences or case presentations

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Requests for reprints should be addressed to Peter G. Bernad, M.D., M.P.H., F.A.C.P., Neurentox International, 2112 F Street NW, Suite 303, Washington, D.C. 20037.

to the entire hospital staff. One such case was recently described in which a young individual died in England but the tissues were stored, and 10 years later this patient was identified as having had AIDS. The very first cases that were seen were noted in patients who presented with Kaposi's sarcoma or Pneumocystis carinii pneumonia.[9] These usually occurred in healthy promiscuous homosexual males. Then in 1981 AIDS was described in intravenous drug users.

From the clinical point of view a patient with HIV infection presents with fever, leukopenia, diminished delayed hypersensitivity, proctitis, perianal ulcerations and lymphadenopathy. Of course, the patient may present with any one or a combination of these symptoms. Some patients present only with depression and altered mental status or with primary neurological syndromes such as difficulty walking. Frequently in the clinical work-up of these patients, there is selective decrease in T lymphocytes as outlined before; specifically the T4 lymphocyte is decreased whereas the T8 lymphocyte, which is the Suppressor/Cytotoxic subset cellular immunity, is elevated.

The neurologic complications of HIV include viral syndromes such as subacute encephalitis and primary cytomegaloviral infection, however, atypical aseptic meningitis is also seen frequently. In addition, herpes simplex encephalitis, progressive multifocal leukoencephalopathy, viral myelitis, varicella zoster infections and HIV dementia are seen. Nonviral infections include the bacterial such as Escherichia coli, the parasites such as Toxoplasma gondii, fungal Candida albicans, Cryptococcus neoformans, coccidioidomycosis, syphilis, atypical mycobacteria and Mycobacterium tuberculosis and Aspergillus fumigatus.

Neoplasms include primary CNS lymphoma, systemic lymphoma with CNS spread and Kaposi's sarcoma. Stroke may be from infarction, hemorrhage or embolus including bacterial and nonbacterial thrombotic strokes, and also arteritis.

Myopathy may show denervation atrophy on biopsy. Inflammatory type of myopathy, polymyositis, type II atrophy or disuse is seen, as well as Nemaline Rod myopathy and even myopathy secondary to treatment such as Zidovudine myopathy. This presents as a proximal muscle weakness; elevated CPK and abnormal mitochondria are seen and "ragged red" fibers on histochemistry. The changes in the muscle may be either direct HIV infection or indirect HIV infection. Cryptococcal disease may cause myositis. Mycobacterium avium-intracellulare will cause an infection and muscle disease. Necrotizing myopathy may be seen and some of these may be secondary to hyperkalemia.

Spinal cord syndromes are known, including vacuolar myelopathy and necrotizing myelopathy. Myeloradiculitis is seen; this usually has a flaccid paraplegia presentation with incontinence and sphincter disturbance.

There are certain risk factors that have been identified over the years for AIDS. These include homosexuality, bisexuality, multiple and repeated infections with syphilis, herpes simplex, herpes zoster and non-B hepatitis. It has also been found that multiple and diverse sexual practices including anal intercourse may be predisposing, as well as IV drug use, frequent transfusions and hemophilia. Haitian immigrants as well as immigrants from certain African countries have a high risk. Infants may develop AIDS, especially those who are born of mothers who have AIDS and infants whose mothers are active prostitutes. I recently saw a 36-year-old male banker; the patient presented with progressive confusion, encephalopathy, paraparesis, dementia, and then progressed to seizures, obtundation and finally coma and death. For 2 years this patient's symptoms were subacute, and then in the last 5 months they were acute, which progressed to death.

## DIAGNOSIS

The diagnosis of AIDS is made on the clinical presentation that frequently suggests a possible diagnosis. Of course, any young person presenting with Pneumocystis carinii pneumonia, Cryptococcal disease, Candida or thrush, herpes simplex infection, cytomegalovirus infection, herpes zoster, syphilis, tuberculosis, atypical TB, hepatitis, amebiasis or general warts indicates a high risk. Diagnostic studies that are done are based on the clinical findings in the history, physical exam and neurologic examination as well as the appropriate history of a member of a high risk group. After the history and physical examination, routine blood work is usually done and then special diagnostic studies including CT and MRI. Computer tomographic scanning may show focal masses, areas of contrast enhancement, or cerebral atrophy.[10,11] The identification of

focal enhancing rings or nodules in the cerebrum on CT scanning indicates toxoplasmosis most likely. However, biopsy is helpful in differential diagnosis and is strongly recommended in most instances since the biopsy may help determine treatment. CT may also show low density nonenhancing areas on CT and this is usually progressive, multifocal leukoencephalopathy. Double dose contrast is helpful and may guide the biopsy needle.

Magnetic resonance imaging may be the first line procedure and has superseded CT scanning because of its well documented sensitivity, especially in white matter lesions. The white matter lesions are very well seen as in, for example, progressive multifocal leukoencephalopathy and HIV infection encephalopathies. Usually in HIV infection encephalomalacia may be seen primarily. Positron emission tomography (PET scan) and single photon emission computerized tomography (SPECT scan) may pick up abnormalities not seen in the MRI or CT scan. It may also help to evaluate asymptomatic patients or HIV positive.

What is quite evident is that the subacute encephalitis represents the most common neurologic complications of HIV infection. Some patients may present with decreased attention, apathy, withdrawal, depression, forgetfulness, loss of concentration and changes in higher cortical functioning, as opposed to any other findings such as in the motor or sensory systems.[12,13] These patients necessarily will need to have HIV testing. It is known that HIV can replicate itself in the central nervous system (CNS) without clinically detectable neurologic dysfunction.[14] Virus has been recovered from cerebral spinal fluid at all periods of infection. The CNS may be the first site for HIV infection and prone to serologic documentation.

The electroencephalogram may be the most important current diagnostic test in the early phases of infection or in the asymptomatic HIV patient. Electroencephalography may also be used to follow the patient clinically or following a treatment protocol. EEG is the only truly functional test evaluating electrical activity of the brain. This test is able to identify abnormalities earlier than the other tests and may be able to identify abnormalities in subclinical disease. The EEG is not pathognomonic for neuroAIDS but is very helpful in evaluating the patients especially in early disease with pseudodepression, focal clinical signs, and seizures. In one study 67% of patients with AIDS had abnormalities on their EEG. Of the patients that did not have AIDS but had AIDS related complex (ARC), 36% had abnormal EEGS. Six patients were asymptomatic.[15] In another study, 27% of HIV infected patients had abnormal EEGs - 25.4% among those who were asymptomatic, and 29.9% of patients with lymphadenopathy.[16]

The most frequent finding on EEG is theta slowing in the frontal or frontotemporal areas.[17–19] Occasionally, as well, delta slowing is seen. Paroxysms with sharp activity may also be found. The generalized or predominantly anterior symmetric slowing has been noted by many researchers. Focal EEG findings and sharp activity associated with a focal central nervous system process such as toxoplasmosis has also been identified.[19] Among other studies, there has even been a report of periodic sharp activity and periodic lateralized epileptiform discharges, which disappeared after the patient received treatment and had clinical improvement.[20–28] Seizures may be a manifestation of HIV.[29]

It is important to remember that the HIV type I has been isolated in cerebral spinal fluid, and this finding did not correlate with blood positivity.[14] Frequently patients with asymptomatic HIV infection may present only with headache.

Viral DNA and RNA has been found in the brains of AIDS patients who died of subacute encephalopathy. HIV type I replicates in the brain. Its presence may not immediately cause neurologic signs or symptoms but potentially may be suspected clinically, and that is the time when an EEG may be very helpful. It may also be said that neuropsychological testing may be useful.[12]

In summary, electroencephalographic studies are sensitive tests but they are nonspecific. Early clinical manifestations of AIDS may include personality change, depression apathy, memory loss. The EEG is useful in the work-up of patients suspected of HIV disease or AIDS. Subacute encephalitis is probably the most common presentation; 90% of these AIDS patients have had subacute encephalitis. Focal brain lesions such as toxoplasmosis and lymphoma may produce focal changes in the EEG. The electroencephalogram may be very important to follow patients in clinical trials during treatment, for example with interferon. Quantitative electroencephalography may also be very useful and may even supplant regular EEGs

because it is able to identify subtle slowing. In one recent study, eight patients were evaluated and six of the patients had abnormalities including increasing theta in the anterior frontal leads. AIDS-dementia was associated with intermittent or continuous slowing, usually anteriorly. The EEGs showed progressive changes and looked somewhat like those associated with dementia of Alzheimer's disease. The electroencephalogram is recommended because of its cost, it is more cost effective than CT scan or MRI, and also because of the ease of administering the test to patients. Other neurophysiologic testing such as long latency event related potentials[30] as well as computerized topographic mapping hold out promise of useful evaluation in patients suspected of HIV disease.[31,32]

Great care must be taken in electroencephalographic labs, and guidelines should be followed.[33–35] Certain blood precautions should be taken, and wound and skin precautions should be taken as well. Gloves are recommended including double gloving, although this may not necessarily be a protection against needles. The equipment needs to be cleaned and no needles should be used in terms of needle electrodes. Disc electrodes should be cleaned with gauze, tap water or mechanical cleaning, or 2% Glutaraldehyde solution for 30 minutes. Steam autoclaving for 121 degrees centigrade times 1 hour or 14 lbs per square inch is recommended. Nasopharyngeal leads are not recommended since HIV type I has been found in saliva. The Grass Corporation has made excellent recommendations in this regard.

HIV infection or AIDS may be diagnosed by using antibody that is detected by immunofluorescence, enzyme-linked immunosorbent assay, or radioimmuno assay or western blot assays.[36]

Human T cell lymphotropic virus is the virus that is thought to cause AIDS. The type I causes acute adult T cell leukemia, as well as tropical spastic paraparesis. It is also known as TSP/HTLV-I associated myelopathy, or as HAM. This causes a chronic disease reminiscent of multiple sclerosis seen primarily in the Caribbean, Japan, and Africa. It was discovered in 1980 and is endemic to the Caribbean, in South America and Panama City, Panama. Antibody is found also in the cerebral spinal fluid in this condition. One seropositive patient had multiple sclerosis but the CSF was negative and antibody positivity was noted to HTLV-I.[37] This has been associated with blood transfusions in the United States.[38]

Human T cell lymphotropic virus type II was discovered 8 years ago: One patient has been described as having exfoliative erythroderma.[39] Three patients have been described as having hairy cell leukemia; this is seen in the blood of IV drug users, frequently in the blighted neighborhoods of Newark, New York and New Orleans. It may be transmitted through blood transfusions. It is thought that it may be the cause of chronic fatigue syndrome or immune dysfunction syndrome, known as chronic fatigue immune dysfunction syndrome (CFIDS). This has also been described as a virus looking for a disease.

Human T cell lymphotropic virus type III is the HIV (Human Immunodeficiency Virus), also known as Human Immunodeficiency Virus-type I as opposed to SIV that is seen in monkeys. In 1991 it is thought to be the most likely cause of AIDS in the U.S.A. It is seen in West Africa and is similar to SIV. This is an RNA virus, has a reverse transcriptase, is a retrovirus, and makes DNA copy of viral RNA.

Human T cell lymphotropic virus type IV is seen in healthy West Africans.[40] The French have termed AIDS as LAV, also known as lymphadenopathy associated virus. Another term used has been AIDS related virus, and AIDS related complex or "ARC." The ARC is somewhat less severe than AIDS, and it is an immune system deterioration without signs of life-threatening opportunistic infections such as Pneumocystis carinii pneumonia, which is the hallmark of AIDS.

From a genetic point of view, there are certain genes that code for the major aspects of this particular virus; the ENV gene is the major envelope gene, codes for GP120, which is the major envelope glycoprotein and essential for virus binding.[41] Then there is the GAG gene that codes for core proteins, and the POE gene that codes reverse transcriptase.

## TREATMENT

In 1991, there is no accepted treatment for AIDS except Azidothymidine (AZT). Zidovudine is the standard therapy for patients with altered immunity due to infection with HIV. It slows the disease process in persons with HIV type I. This is given when the CD4 count is less than 500 cells per cubic mm. Although initially this drug was given only to patients with

advanced disease, more recently it is effective in treating patients with low helper T cell levels.[42] A related compound, nucleoside analogue dideoxyinosine (DDI), has been made available to HIV infected patients through the expanded access program of the Federal Drug Administration.

There is specific treatment for the various infections, however. Specifically, cytomegalovirus infection has been treated with ganciclovir, and ganciclovir has been helpful in treating the retinitis, and gastrointestinal problems. Unfortunately, this particular treatment causes neutropenia. Sodium phosphonformate (Foscarnet) has been used. This inhibits the function of the DNA synthetic enzymes. Its herpes virus DNA polymerases. HIV reverse transcriptase unfortunately has a short half life. Pyrimethamine and Sulfadiazine is the treatment of choice for toxoplasmosis. ARA-A or Acyclovir is used in herpes infections and Amphotericin B and 5-Flourocytosine in the infection with Candida or other fungi. An Ommaya reservoir may be used. Specific antibiotics such as penicillin are used for treatment of syphilis.

For TB, INH, Ethambutol, and Rifampin are treatments. For certain kinds of tumors and malignancies, radiation therapy may be the treatment of choice, and finally for focal lesions, such as focal infection with toxoplasmosis, surgery is recommended. Biopsy is frequently important because, depending on the findings, treatment may vary.

Great strides have been made, but there is even more to learn before this devastating world-wide disease is cured or even well controlled.

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