Neuropsychiatric AIDS and Neurosyphilis: Overlap

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The intent of this paper is to argue 1) that neuropsychiatric AIDS, often referred to as "AIDS Dementia", is in fact seronegative neurosyphilis and often dramatic clinical resolution of "AIDS Dementia" will result from appropriate treatment for neurosyphilis; 2) seronegative neurosyphilis can present in the HIV (Human Immunodeficiency Virus) positive patient with only subtle clinical signs and must be carefully looked for by the clinician; and 3) that *all* patients with AIDS and any central nervous system (CNS) findings on physical examination should be assumed to have and must be treated appropriately for neurosyphilis.

Dementia, as well as a variety of other neuropsychiatric syndromes, has been recognized as a common complication of AIDS from the time the disease was originally defined.[1] In fact, it has been recently postulated that central nervous system findings may often represent the initial manifestation of AIDS.[2]

A patient, especially one positive for the Human Immunodeficiency Virus,[3] may be seronegative for syphilis in serum and cerebral spinal fluid (CSF) and also have active neurosyphilis[4 5], or active syphilis in general.[6 7 8 9]

I wish to report five AIDS patients all of whom carried a diagnosis of neuropsychiatric AIDS/AIDS Dementia, but whose neuropsychiatric impairment responded dramatically to vigorous treatment for neurosyphilis despite non-diagnostic serologic studies for syphilis. As many patients with seronegative neurosyphilis present with subtle clinical signs or symptoms thus making the diagnosis difficult,[10 11] it would seem medically prudent to vigorously investigate the possibility that any AIDS patient with neurologic abnormalities may have seronegative neurosyphilis and, if clinically warranted in the opinion of the attending physician, treat accordingly.

Patient One

Patient One presented in October 1986 as a 36 year old right handed physician complaining of gradually increasing loss of function of the left lower extremity associated with intermittent lancinating pains from that extremity which had begun six to eight months previously. Upon careful questioning, the patient also admitted to recent problems with short-term memory; inability to concentrate for what would have been extended, but normal periods of time; hyper-irritability; intermittent global headaches; severe malaise and fatigue; depression and anxiety requiring psychiatric intervention; insomnia; and severe diminution of his libido. The patient considered himself sufficiently disabled that he had temporarily suspended the practice of medicine. There was no history of prior neurologic disease and past medical history in general was unremarkable. The only medicine being used was a benzodiazapine class tranquillizer/ hypnotic. The patient denied illicit drug use, but was a member of a high risk AIDS group. There was a history of multiple potential exposures to HIV. There was a negative history of syphilis.

Physical examination revealed an afe-rile, thin, but well nourished white male, appearing younger than his stated age and in no obvious distress. Moderate generalized lymphadenopathy of the cervical, sub-mandibular, occipital, axillary and inguinal regions was present. Minimal oro-pharyngeal candidiasis was observed. Pupils responded sluggishly to light, but normally to accommodation. The left patellar reflex was absent. The patient walked with a slightly broadened gait and heal to toe was performed with difficulty and

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some drifting to the left. There was no evidence of muscle wasting, including those of the left lower extremity. The patient's attention span seemed short and a definite sense of inappropriate anger and hostility was conveyed. Topics mentioned at the beginning of the interview could not be recalled at the end of the interview. Cognitive abilities seemed grossly normal. A lumbar puncture was performed as part of the medical evaluation.

HIV Studies:

Serum: Positive by both ELISA and Western Blot techniques.

CSF: Positive by both ELISA and Western Blot techniques.

Syphilis Serologies:

Serum: VDRL, FTA-ABS and MHA-TP all non-reactive.

CSF: VDRL and FTA-ABS both non-reactive. MHA-TP not done.

Other laboratory data:

CSF: No cells present. Circulating Immune Complexes of the IgG class at a level of 400 mg/dl (normal range less than 9.1 mg/dl). All usual studies normal or negative.

Serum: Ferritin = 535 ng/ml (normal to 230 ng/ml). Beta-2-Microglobulins = 3.0 mg/L (normal to 2.5 mg/L). Globulins = 4.0 g/dl (normal to 3.5 g/dl).

Immune Parameters:		
Total WBC Count	6,400	
Total Lymphocyte Count	1,478	23.1%
Total B Lymphocytes	118	8.0%
Total T Lymphocytes (Til)	1,168	79.0%
T4 (Helper/Inducer)	310	21.0%
T8 (Suppressor/Cytotoxic)	576	39.0%
T4/T8 Ratio		0.54

The patient was treated for ten days with a constant intravenous infusion of Penicillin G Sodium at a dose of 25,000,000 units per day. This was followed by Doxycycline 400 mg by mouth per day in two divided doses for one year. The patient is presently receiving a maintenance/prophylactic dose of 200 mg Doxycycline per day.

The patient began experiencing remission of his various symptoms by the end of the first ten days of treatment. Currently, the patient is again fully employed with an active medical practice. His left leg is normal by both subjective and clinical parameters. The patella reflex is now present and equal to that on the contralateral side. Pupils are normally reactive to light as well as accommodations. The patient's memory is normal; his depression and anxiety have cleared no longer requiring psychiatric intervention; there is no indication of inappropriateness of affect; and the insomnia has improved. The headaches have resolved and the patient reports that his libido has returned. Energy and exertional tolerance are normal. Minor lymphadenopathy persists. There is no clinical evidence of oropharyngeal candidiasis.

Patient Two

Patient Two was a 42 year old left handed businessman with Pneumocystis Carinii Pneumonitis; disseminated atypical Tuberculosis (Mycobacterium Avium Intracellulare); anergy with severe immune depression; and severe vegetative AIDS dementia with cerebral atrophy. The patient was disoriented to person, place and time. All higher cognitive functions were lost. The patient could not perform simple calculations or in any manner carry on a conversation. He recognized no one and was incontinent of both urine and feces. He was unable to feed or in any way care for himself. Private duty nursing was present twenty-four hours per day. There was a clear history of multiple potential exposures to HIV. There was also a history of syphilis diagnosed and treated approximately 15 years in the past. A lumbar puncture and a CT Scan of the head with and without contrast enhancement were performed as elements of the work-up.

HIV Studies:

Serum: Positive by both ELISA and Western Blot techniques.

CSF: Positive by both ELISA and Western Blot techniques.

Syphilis Serologies:

Serum: VDRL and FTA-ABS non-reactive.

CSF: VDRL and FTA-ABS non-reactive.

Other Laboratory Data:

Blood: WBC = 1,900/cu mm; HGB = 6.1 gr/dl; ESR = 147 mm/hr; C-reactive protein = 92.3 mg/L (normal to 12 mg/L);

globulin = 3.9 gr/dl; ferritin = 1434 mcg/L; cholesterol = 94 mg/dl; calcium = 8.9 mg/dl.

CSF: No cells present. Protein elevated. No evidence of any AIDS related opportunistic infections involving the CNS.

CT of head with and without contrast: Significant cortical and cerebellar involution without enhancing lesion, mass effect or midline shift.

Immune Parameters:

Total WBC Count	1,900	
Total Lymphocyte Count	540	27.0%
Total B Lymphocytes	44	8.1%
Total T Lymphocytes (Tl 1)	346	64.0%
T4 (Helper/Inducer)	32	6.0%
T8 (Suppressor/Cytotoxic)	103	19.0%
T4/T8 Ratio		0.31

The patient, although clearly *in extremis*, was begun on a continuous intravenous infusion of Penicillin G Sodium at a dose of 40,000,000 units per day. By the end of the fifth day of treatment, the patient was lucid, coherent and out of bed at will without assistance. Specifically, once oriented, he remained oriented to person, place and time. He was no longer incontinent of either urine or feces and would appropriately seek bathroom facilities. He was able to recall, recognize and hold conversations with individuals, including his attending physician, whom he had known for years, but not recognized for months. He was able to read the daily newspaper and comment properly on stories that interested him. He could feed himself, care for other simple personal needs, and would sit at table with guests for meals. He was able to watch television and — under my observation — would laugh or otherwise respond to what he was seeing in a logical and appropriate fashion. On day five, the patient's FTA-ABS in serum converted to weakly reactive.

This patient surely represents the extreme of what we have been calling "AIDS Dementia". That is, a total vegetative state. Yet within a period of days all who observed his progress were amazed and astonished by the recovery of his central nervous system faculties. Unfortunately for this individual, however, there was no immune reserve left to him and he ultimately died of overwhelming Pneumocystis Carinii pneumonia. Pathetically, he died with a clear sensorium.

Patient Three

Patient Three is a 32 year old right handed male who for almost ten years has functioned as a successful real estate broker. Upon presentation, his chief complaint was the gradual, but increasingly accelerating loss of his cognitive and emotional skills. Routine sedentary concentration was impossible. He admitted to not having read a newspaper or a novel for several months. The patient's short term memory was severely affected. He was unable to remember and therefore keep appointments. He had also noticed a marked increase in his tendency to become irritable and easily infuriated and commented that others in his office had noticed this about him and had mentioned it to him. Depression, not suicidal in nature, was a new and very serious problem. The patient further complained of a decrease in his libido and a dramatic lowering of his exertional tolerance. The patient felt he was quickly nearing the time when he would not be able to function professionally and was preparing the way for permanent and total disability. The patient is a member of an AIDS risk group, but denied ever having been diagnosed with or treated for syphilis. Lumbar puncture was not performed.

On physical examination, the patient was a well developed, well nourished white male in no acute distress, febrile to 99.0°. His affect was humourless, depressed and flat. It was difficult for him to recall recent facts or events, although with effort he could do so. Diffuse, minimal lymphadenopathy was present. Argyll-Robertson pupils were present bilaterally. Other physical and neurologic parameters were grossly normal. There was no clinical evidence of opportunistic infection.

HIV Studies:

Serum: Positive in April 1987 by both ELISA and Western Blot techniques.

Syphilis Serologies:

Serum: VDRL and FTA-ABS both non-reactive.

Other Laboratory Data:

Serum: Neopterin = 13.8 nmol/L (normal to 10.0 nmol/L); calcium = 9.3 mg/dl; random cholesterol = 176 mg/dl.

Immune Parameters:

Total WBC Count	4,800	
Total Lymphocyte Count	1,790	37.3%
Total B Lymphocytes	90	5.0%
Total T Lymphocytes (Til)	1,504	84.0%
T4 (Helper/Inducer)	376	21.0%
T8 (Suppressor/Cytotoxic)	823	46.0%
T4/T8 Ratio		0.46

The patient was immediately placed on Doxycycline 400 mg by mouth per day in two divided doses. This regimen was well tolerated. When reevaluated one month following his initial visit and the institution of therapy, the patient reported that his memory, ability to concentrate and easy irritability were dramatically improved. He commented that others in his office had remarked on the change. He was working a full-time schedule and had abandoned his prior intention of seeking disability status. His affect was pleasant, responsive and characterized by appropriate humour. He continued to report that he did not yet consider his libido normal. His cognitive abilities were clearly normal. His Argyll-Robertson pupils were no longer present, although his pupils were sluggishly responsive to light bilaterally. The patient continues on Doxycycline at a dose of 400 mg per day.

Patient Four

Patient Four is a 30 year old right handed Vice President of a savings bank who at the time of evaluation was disabled unable to carry on his employment related duties. He was unable to remember from one day to the next the events of routine meetings; he could not remember to perform various simple but necessary functions at the bank which he had been doing automatically for several years. While he did not have a history of emotional instability, he was experiencing a depression characterized by suicidal ideation along with severe free floating anxiety requiring not only psychiatric intervention, but anti-depressant medication as well. His personal care and hygiene had deteriorated to the point where he had to be looked after by friends on a constant basis. Although a resident of New York City for years, he was unable to find my office by himself and had to be brought by a friend. Heightened irritability leading to fits of explosive anger further impaired his professional and social skills making it impossible to carry on normal interpersonal relationships. He further complained of impotence and increasing insomnia. He is a member of a high risk AIDS group, but there was no documentation of his ever having been diagnosed with or treated for syphilis. There was a negative history of opportunistic infections or any other AIDS related conditions. As part of his evaluation, CT Scan of the head and sinuses with and without contrast was performed. Lumbar puncture was not performed.

Physical examination revealed an afebrile, thin, but properly nourished white male constantly restless, constantly in motion and with an attention span measurable in seconds. The patient was unable to recall things said to him even minutes earlier. Following simple commands was difficult for him, although it was apparent he was trying to be cooperative. His affect and mood were severely depressed. He was clearly extremely and inappropriately anxious. Pupils were sluggish to light, but not to accommodation. No other neurologic deficits could be elicited. Moderate, generalized lymphadenopathy was also found on physical examination.

HIV Studies:

Serum: Positive by both ELISA and Western Blot techniques.

Syphilis Serologies:

Serum: VDRL and FTA-ABS both repeatedly non-reactive.

Other Laboratory Data:

CT of Head: Ventricular and sulcal dilation with involution of the cortex, cerebrum and cerebellum.

Immune Parameters:

Total WBC Count	4,800	
Total Lymphocyte Count	1,100	37.3%
Total T Lymphocytes (T11)	906	82.4%
T4 (Helper/Inducer)	229	20.8%
T8 (Suppressor/Cytotoxic)	523	47.6%
T4/T8 Ratio		0.43

The patient was placed on Doxycycline 400 mg by mouth daily in two divided doses. The medicine was well tolerated. Within six weeks the patient had returned

to full time work having resumed all of his former duties at the savings bank. The antidepressant medicine has been discontinued, but the patient continues to see his psychiatrist on a regular basis. The anxiety, irritability and depression have resolved. The patient rates his memory as near normal. On a one-to-one encounter, the patient is clearly calmer and in more control. He follows commands easily. Pupils are less sluggish to light. He no longer requires assistance in travelling or in caring for himself. He remains on Doxycycline.

Patient Five

Patient Five is a 29 year old left handed public relations specialist for a New York City concern. When initially evaluated, the patient was complaining of depression and fatigue severe enough to interfere with his ability to function at work. He freely admitted that his ideation was paranoid and related that this too was making it increasingly difficult for him to perform professionally. Serious problems with his short-term memory ("I can't remember a thing") also impaired his professional life. His social life was virtually nonexistent and he was becoming increasingly isolated from friends and acquaintances. Severe, disabling headaches, described by him as migrainous, were virtually daily in frequency and required narcotic analgesia for relief. Sedatives and hypnotics were also used at bedtime to combat a worsening insomnia and induce sleep. The patient's libido was reported as seriously impaired. He was a member of a high risk AIDS group, but had never been told he had or had been treated for syphilis. As part of the medical evaluation, lumbar puncture was performed.

On physical examination, the patient was febrile to 99.4°. He had moderate generalized lymphadenopathy of the cervical, submandibular, axillary and inguinal regions. Slight oro-pharyngeal candidiasis was present. Cognitive skills appeared grossly normal although the patient's affect was severely depressed and he was complaining of a disabling headache. Pupils were sluggishly reactive to light and normally reactive to accommodation. Otherwise, the physical examination was within
normal limits.

HIV Studies:

Serum: Repeatedly positive by both ELISA and Western Blot techniques.

CSF: Positive by both ELISA and Western Blot techniques.

Syphilis Serologies:

Serum: VDRL and FTA-ABS both repeatedly non-reactive.

CSF: VDRL and FTA-ABS both non-reactive.

Other Laboratory Data:

Serum: Neopterin = 12.7 nmol/L; globulin = 4.3 gr/dl; cryptococcal antigen negative; toxoplasmosis antibody IgM class negative.

Immune Parameters:

Total WBC Count	6,100	
Total Lymphocyte Count	1,939	31.8%
Total B Lymphocytes	78	4.0%
Total T Lymphocytes (Til)	1,163	60.0%
T4 (Helper/Inducer)	271	14.0%
T8 (Suppressor/Cytotoxic)	368	19.0%
T4/T8 Ratio		0.74

The patient was placed on daily injections (Monday through Friday) of Procaine Penicillin 2,400,000 units per injection for three weeks. This was followed by Doxycycline 400 mg daily by mouth in two divided doses for three months. The patient remains on maintenance Doxycycline at a dose of 200 mg daily.

The patient's headaches have significantly improved in both severity and frequency now requiring only non-narcotic analgesia for relief. He is fully employed carrying on all of his professional responsibilities. In fact, he was recently granted a promotion within his firm. His depression has cleared. The anxiety and hyper-irritability are now gone. The patient rates his exercise and exertional tolerance as normal. He sleeps well requiring no sedative or hypnotic medication. He leads an active and satisfying social life. The oro-pharyngeal candidiasis has resolved and the moderate lymphadenopathy observed initially is now minimal. The patient has been afebrile for several months.

I have attempted to present a clinical spectrum of AIDS patients with various central nervous system findings ranging

from a totally vegetative state (Patient Two) to lesser and far more subtle forms of nervous system involvement (Patient Five). That neurosyphilis can present in subtle and unusual ways and, therefore, be overlooked by the clinician is, of course, well known.[12] That neurosyphilis can likewise present with non-reactive serologies in both serum and cerebral spinal fluid is also accepted.[13] Further, that the incidence of seronegativity for syphilis increases dramatically in individuals with concomitant HIV infection has recently been demonstrated.[14]

The conclusion that must be drawn from the literature as the literature applies to the five patients presented in this paper is inescapable: In the HIV positive individual with even subtle neurologic findings, it is impossible — given present day technology — to rule out neurosyphilis. Therefore, in such a patient, unless another medically acceptable explanation can be found that accounts for the observed neu-rolgic deficit, a presumptive diagnosis of neurosyphilis must be made and, barring any contraindictions, appropriate therapy instituted. This becomes especially pertinent if it is remembered that — as can be gleaned from the five patients presented above — the therapy for neurosyphilis is relatively easy, benign and harmless. Further, it can be delivered on an ambulatory basis.

We are told that AIDS ultimately has a mortality approaching 100%. Given this harsh reality, and given the easy reversibility of neurosyphilis in the AIDS patient, do we not owe our patients the benefit of the doubt? In my opinion, it is remiss of the physician attending an AIDS patient with neurologic dysfunction not to aggressively look for and vigorously treat neuro-syphilis.

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