Frequency of Neurological Involvement in Human Immunodeficiency Virus Infected Patients and Evaluation of the Patients for AIDS Dementia Complex

İnsan İmmün Yetmezlik Virüsü ile Enfekte Olgularda Nörolojik Tutulum Sıklığı ve Bu Olguların AIDS Demans Kompleksi Açısından Değerlendirilmesi

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This study was presented as a poster in IUMS (Meetings of the Three Divisions of the International Union of Microbiological Societies) 2008, 14th International Congress of Virology 10 – 15 August 2008, Istanbul, Turkey.

Geliş Tarihi/*Received:* 12.06.2008
Kabul Tarihi/*Accepted:* 01.05.2009

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ABSTRACT Objective: Studies on neurological involvement in patients with human immunodeficiency virus (HIV) infection in Turkey are lacking. This study was designed to determine the frequency and spectrum of neurological complications in HIV infected cases, to evaluate the patients for AIDS dementia complex and to determine the parameters associated with neurological involvement. **Material and Methods:** During a 6-month period, 20 consecutive patients with HIV infection were recruited to this prospective study. In addition to routine follow-up, motor dysfunction, behavioral abnormalities and cognitive impairment were carried out in all patients and CD4+ T lymphocyte count and plasma HIV-1 RNA were investigated at the time of the study. Results were statistically compared for age, duration of illness, CD4+ T lymphocyte count, sex, concurrent diseases and antiretroviral therapy. **Results:** In 15% of the patients, neurological symptoms constituted the initial presentation. Neurological complications were present in 6 (30%) patients and they were as follows: cerebral tuberculoma, ischemic serebrovascular disease, progressive multifocal leukoencephalopathy, AIDS dementia complex, AIDS dementia complex and mononeuropathy multiplex, and AIDS dementia complex and distal symmetric polyneuropathy. More than one neurological disease was detected in two cases. All patients were at AIDS stage and median CD4+ T lymphocyte count was 105 cells/mm^3. AIDS dementia complex was detected in three patients (two had motor dysfunction and one had cognitive impairment). When compared with cases with no neurological involvement, significant parameters associated with neurological involvement and AIDS dementia complex were low CD4+ T lymphocyte count, not receiving highly active antiretroviral therapy or low adherence to therapy. **Conclusion:** Detection of neurological diseases in approximately one third of the patients in this study showed that, such complications were also frequent and important in Turkish HIV infected patients and this topic needed more attention.

Key Words: HIV infections; AIDS dementia complex; neurological manifestations; acquired immunodeficiency syndrome

ÖZET Amaç: Türkiye'de HIV enfekte olgulardaki nörolojik tutulum ile ilgili çalışmalar azdır. Bu çalışma, insan immün yetmezlik virüsü ile enfekte olan olgularda nörolojik tutulum sıklığının ve görülen hastalıkların spektrumunun araştırılması, olguların AIDS demans kompleksi açısından değerlendirilmesi ve nörolojik tutulum ile ilişkili parametrelerin saptanması için planlanmıştır. **Gereç ve Yöntemler:** Bu prospektif çalışmaya 6 aylık süre içinde, birbiri ardına başvuran 20 HIV enfekte olgu alınmıştır. Rutin izleme ek olarak tüm olgular motor disfonksiyon, davranışsal ve bilişsel bozukluk açısından incelenmiş ve çalışma sırasındaki plazma HIV-1 RNA ve CD4+ T lenfositi düzeyleri araştırılmıştır. Sonuçlar istatistiksel olarak yaş, hastalık süresi, CD4+ T lenfositi sayısı, cinsiyet, eşlik eden hastalıklar ve antiretroviral tedavi açısından karşılaştırılmıştır. **Bulgular:** Olguların %15'inde nörolojik semptomlar ilk başvuru nedeni idi. Nörolojik komplikasyonlar serebral tüberkülom, iskemik serebrovasküler olay, progresif multifokal lökoensefalopati, AIDS demans kompleksi, AIDS demans kompleksi ile mononöropati multipleks ve AIDS demans kompleksi ile distal simetrik nöropati olmak üzere 6 (%30) olguda saptandı. İki olguda birden fazla nörolojik hastalık mevcuttu. Olguların tümü AIDS evresinde ve ortalama CD4+ T lenfosit sayısı 105 hücre/mm^3 idi. AIDS demans kompleksi 3 olguda (2 olguda motor disfonksiyon ve bir olguda bilişsel kayıp nedeni ile) saptandı. Nörolojik tutulumu olmayan olgular ile karşılaştırıldığında, nörolojik tutulum ve AIDS demans kompleksi ile anlamlı ilişki sergileyen parametreler, düşük CD4+ T lenfosit sayısı, antiretroviral tedavi kullanılmaması ve düzensiz antiretroviral tedavi kullanımı olarak saptandı. **Sonuç:** Bu çalışmada, olguların yaklaşık 1/3'ünde nörolojik hastalık saptanmış olması, HIV enfekte Türk olgularda da bu komplikasyonların sık ve önemli olduğunu ve bu konuya daha fazla dikkat edilmesi gerektiğini göstermiştir.

Anahtar Kelimeler: HIV enfeksiyonu; AIDS; Nörolojik bulgular; AIDS demans kompleksi

Turkiye Klinikleri J Med Sci 2009;29(6):1473-82

The nervous system is frequently involved in patients infected with human immunodeficiency virus (HIV). Neurological complications constitute the initial presentation in 10% of patients and occur in 30 to 50% of patients during the course of the disease. In autopsy studies, however, involvement of the nervous system is reported in up to 80% of the cases.[1,2]

Causes of neurological disease in HIV infected patients can be reviewed in two groups: Primary HIV infection-related syndromes are dementia, neuropathy and myelopathy and secondary complications are opportunistic infections [such as toxoplasmosis, cryptococcosis, cytomegalovirus (CMV) infection, and progressive multifocal leukoencephalopathy (PML)], inflammatory conditions, drug toxicity, primary and metastatic neoplasms, metabolic and nutritional disorders, and cerebrovascular disease.[2, 3]

AIDS dementia complex (ADC), also called as subacute encephalitis, HIV encephalopathy, multinucleate giant cell encephalitis, and HIV-1 associated cognitive/motor complex, is among the most common neurological complications.[1,3] Its prevalence in AIDS patients is reported as 15%, and it is the primary AIDS defining illness in 3-10%.[1] Symptoms can be categorized in three groups:

1. Cognitive (forgetfulness, mental slowing, and poor concentration),

2. Motor (gait disturbance, imbalance, clumsiness, weakness, and poor coordination),

3. Behavioral (apathy and diminished desire for social contact). The symptoms and signs are subtle early in the presentation and neuropsychologic tests are useful in identifying patients with cognitive impairment. Later on, as dementia progresses, cognitive impairment accompanied with psychomotor retardation and severe behavioral abnormalities becomes prominent and objective neurological symptoms such as paraparesia, incontinence, and tremor are seen more frequently.[3] There are no laboratory or neuroimaging study results that are specific for ADC, and the diagnosis relies on exclusion of other causes.[1, 3]

Frequency of neurological complications and spectrum of neurological diseases in HIV infected cases in Turkey are unknown. Although the number of patients in this study was limited, the purpose of this study was to determine the frequency and spectrum of the neurological complications in HIV infected patients and to review them for the presence of ADC.

MATERIAL AND METHODS

In a 6-month period from February to July 2003, in Atatürk Training and Research Hospital, İzmir, Turkey, 20 consecutive patients (18 males, 2 females) with HIV infection were recruited to this prospective study after they provided their informed consents. Local ethics committee approved the study. The average age was 37 ± 12 years (17 to 70 years). Fifteen cases were outpatients and five were inpatients. Eighteen cases were follow-up patients and two (case 14 and 19) were new admissions.

Detailed history of all the patients were recorded including medical, neurological, behavioral, and psychiatric history, information concerning education, trauma, toxic drugs, drug abuse, risk factors for HIV infection, duration of HIV infection, clinical onset of infection, highly active antiretroviral therapy (HAART), hospital stay, coexisting diseases, nutritional habits, and family history. In addition to routine physical examination (including ophtalmologic examination and gynecologic examination in female patients) neurological examination for motor dysfunction, psychiatric examination for behavioral abnormalities were done and mini-mental state examination (MMSE) test and frontal lobe function tests for cognitive impairment were applied to all patients by the same physicians. Using the MMSE test, which consists of 28 questions and has no time limitations, orientation (7 points), attention (9 points), general knowledge (10 points), remote memory (12 points), short-term memory (9 points), and high cortical functions (12 points) were evaluated. The highest score that could be obtained from the test was 59 and scores less then 44 were considered as significant for cognitive impairment. Using frontal lobe function tests, high cortical functions (categoriza-

tion and verbal fluency) were evaluated. Electromyography (EMG) and electroencephalography were performed in 4 cases due to motor abnormalities and in 1 case because of sensory abnormalities found on neurological examination.

The diagnosis of ADC was based on proven HIV infection, presence of acquired neurological loss (clinical abnormality in cognitive, motor or behavioral functions) and exclusion of other neurological or psychiatric illnesses, which can cause such abnormalities. Patients with ADC were staged according to Price and Brew:[4]

Stage 0 (normal): Normal mental and motor function, Stage 0.5 (equivocal/subclinical): Symptoms may be absent, minimal, or equivocal, with no impairment of work or performance of activities in daily living. Mild signs (slowed ocular or extremity movements) may be present. Gait and strength are normal.

Stage 1 (mild): Patient is able to perform all but the more demanding aspects of work or activities of daily living.

Stage 2 (moderate): Patient is able to perform basic activities of self-care but cannot work or maintain the more demanding aspects of daily life. Patient is ambulatory but may require a single prop.

Stage 3 (severe): Patient has major intellectual incapacity and motor disability and is not able to walk without assistance.

Stage 4 (end stage): Patient is in a nearly vegetative state.

In addition to routine laboratory tests, the following tests were performed in all patients: vitamin B_{12}, folic acid, thyroid function tests, serum iron and iron binding capacity, liver function tests, blood urea nitrogen, creatinin, electrolytes, creatinine kinase, lactic dehydrogenase, VDRL, anti-toxoplasma, anti-CMV and anti-herpes virus IgM and IgG, CD4+ T lymphocyte count with flow cytometry and plasma HIV-1 RNA with reverse transcriptase polymerase chain reaction (RT-PCR). The patients were staged according to the Centers for Disease Control and Prevention (CDC) 1993 revised classification system.[5]

For cranial magnetic resonance imaging (MRI) General Electric Vectra 0.5 Tesla was used and 0.1 mmol/kg intravenous gadolinium was given for contrast. All images were evaluated by the same radiologist.

Results were statistically analyzed using SPSS 14.0 for Windows. Descriptive statistical analysis and due to the limited number of patients, non-parametric tests were used for the analysis. For numeric variables (age, duration of illness and CD4+ T lymphocyte count) Mann-Whitney U test and for dicotom parameters (sex, accompanying diseases and antiretroviral therapy) Fisher's Exact Chi-Square test were used. Values of $p< 0.05$ were considered statistically significant. (Statistical analyses were performed in Aegean University Faculty of Medicine Department of Biostatistics).

RESULTS

Characteristics of 20 cases were shown in Table 1. According to the CDC 1993 revised classification system[5], three cases were A1, 6 cases were A2, 2 cases were A3, 1 case was B1, 1 case was B3, 1 case was C1, 1 case was C2 and 5 cases were C3. Ten patients (Cases 3, 4, 7, 12-17, and 19) were at the AIDS stage.

TABLE 1: Characteristics of 20 human immunodeficiency virus infected patients.

Parameter	Results
Sex	18 males, 2 females
Age (years)	17-70 (mean 37.1 ± 12.3)
Duration of HIV infection (months)	4-109 (mean 41.5 ± 32.0)
Number of cases hospitalized	5 (Cases 4, 14, 15, 16 and 19)
CD4+ T lymphocyte count (cells/mm^3)	50-1,592 (mean 383)
Highly active antiretroviral therapy	
Number of naive cases	2 (Cases 12 and 19)
Number of cases with high adherence	12 (Cases 1-6, 9-11, 13, 18 and 20)
Number of non-adherent cases	6 (Cases 7-8 and 14-17)
Education	
University	1 (Case 1)
High school	9 (Cases 3-5, 11 and 16-20)
Secondary school	2 (Cases 7 and 14)
Elementary school	7 (Cases 2, 6, 8-10, 12 and 15)
No education	1 (Case 13)

Nine (45%) cases had one or more co-existing diseases, such as pulmonary tuberculosis, tuberculous lymphadenitis, oropharyngeal *Candida* infection, devastating diarrhea, uveitis, zona zoster or syphilis. Three (15%) cases presented initially with neurological complaints. They were intentional tremor in case 13; forgetfulness, weakness, numbness of hands and feet, imbalance, vertigo, fecal and urine incontinence, gait disturbances, and language impairment in case 15; and gait disturbances, language impairment, loss of coordination, forgetfulness, and fecal and urine incontinence in case 19. Eight cases had motor dysfunction and/or sensory abnormalities on neurological examination. On cognitive evaluation, however, only 1 case was normal, although he was 1 of the patients with neurological involvement. Seventeen cases had mild and 2 cases had significant cognitive impairment. Overall, 9 patients had pathologic findings on cranial magnetic resonance imaging (MRI). The most common finding was cerebral and cerebellar atrophy (3 cases) followed by hyperintense lesions on T2-weighted images (2 cases) and hydrocephaly (2 cases). Electromyography was planned for 4 cases, which was normal in 2 cases and revealed mononeuropathy multiplex in 1 case. The 4th case could not tolerate EMG, but based on clinical findings distal sensorial polyneuropathy (DSP) was diagnosed. Electroencephalography was performed in 1 case and it revealed superficial sleep. Biochemical and serologic tests were not significant. Summary of the findings were presented in Table 2.

Fourteen patients had no neurological involvement. Motor dysfunctions and/or sensory abnormalities found in 3 cases were not considered HIV-related neurological complications; because hearing loss, hypoactivity of the patellar reflex and loss of vision were due to sequela of chronic otitis media, lumbal discopathy and sequela of uveitis respectively. On cognitive evaluation, no patient could receive the total 59 points on the MMSE test. The most prominent impairment was in the area of short-term memory. Thirteen cases had mild and 1 case had severe impairment of short-term memory. Mild impairments of attention, remote memory, frontal lobe function tests, orientation, high cortical functions, and mathematical skills were found in 9, 5, 4, 3, 3 and 2 of the cases, respectively. In 1 case, moderate impairment of attention was detected. Since no patients had less then 44 points on the MMSE test, none was considered to have significant cognitive impairment. In 2 patients (cases 14 and 20), cognitive impairments were related

TABLE 2: Summary of findings in 20 human immunodeficiency virus infected patients.

Feature	Cases without neurological involvement n= 14	Cases with neurological involvement n= 6	Total number of patients
Initial presentation with neurological complaint	-	Cases 13, 15 and 19	3
Motor dysfunction and/or sensory abnormality	Cases 3, 5 and 8	Cases 7, 13, 15, 17 and 19	8
Cognitive evaluation			
Normal	-	Case 7	1
Mild impairment	Cases 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13 and 14	Cases 13, 17 and 19	17
Severe impairment	-	Cases 15 and 16	2
Pathologic findings on cranial MRI*	Cases 3, 4, 5 and 8	Cases 7, 13, 15, 16 and 19	9
Electromyography (in 4 cases)			
Normal	Case 5	Case 17	4
Mononeuritis multiplex	-	Case 16	
Not tolerated	-	Case 19	
Electroencephalography (in 1 case)	-	Case 15	1
Co-existing diseases	Cases 3, 4, 8 and 14	Cases 7, 13, 15, 16 and 19	9

*Magnetic resonance imaging

to depression and antidepressant therapy was initiated. Cranial MRI findings of cerebral and cerebellar atrophy, and nonspecific hyperintense lesions on T2-weighted images were considered changes due to HIV infection. Most of the patients were highly adherent to HAART and 1 case was antiretroviral naive. Co-existing diseases were found in 4 cases. The characteristics of the patients without neurological impairment were shown in Table 3.

Six (30%) patients had neurological diseases. In 2 patients, more than one neurological disease was detected. The most common neurological disease was ADC and was found in 3 cases. In 2 patients with ADC, other neurological diseases, mononeuropathy multiplex or DSP, were detected concomitantly. The remaining neurological diseases were opportunistic infections of the central nervous system (namely cerebral tuberculoma, and PML each in 1 case), and ischemic cerebrovascular disease in 1 case. The mean age, CD4+ T lymphocyte count, plasma HIV-1 RNA, and duration of HIV infection of the 6 patients were 41 years, 105 cells/mm^3, 26.000 copies/mL and 67 months, respectively. Accompanying diseases were present in 5 of the 6 patients. Severe cognitive impairment was found in 2 cases with the diagnosis of PML and ADC. One of the patients with neurological involvement was normal in cognitive evaluation and in another patient cranial MRI was normal. The adherence of the patients to HAART was low (1 out of 5) and 1 patient was antiretroviral naive. During the follow up, 1 patient died on day 60 of admission because of PML. The general characteristics and the results of neurological evaluation of these patients were shown in Tables 4 and 5, respectively.

Review of the patients with ADC in more detail revealed that they all were male, had AIDS (Stage C3), and had detectable plasma HIV-1 RNA levels. Cognitive impairment in case 16, and motor dysfunctions in cases 17 and 19 could not be attributed to other etiologic factors and the clinical staging showed that they had mild, subclinical and severe ADC, respectively. Presence of ADC in case 17, who was a young boy with a short duration of HIV infection, was related to transfusion of contaminated blood.

CD4+ T lymphocyte count and the number of patients who were adherent to HAART were significantly low among patients with neurological

TABLE 3: Characteristics of 14 human immunodeficiency virus infected patients without neurological involvement.

Feature	Results
Sex	13 males, 1 female
Age	24-47 years
CD4+ T lymphocyte count cells/mm^3	65-1,592
Plasma HIV-1 RNA copies/mL	<50-> 75.000
Duration of HIV infection	4-73 months
Evaluation for motor dysfunction and sensory abnormalities	Normal: 11 cases
	Hearing loss: 1 case (case 3)
	Hypoactivity of right patellar reflex: 1 case (case 5)
	Loss of vision: 1 case (case 8)
Cognitive evaluation:	45-57 points (mean: 51 points)
Mini Mental State Examination Test (Total 59 points)	
Cranial magnetic resonance imaging	Normal: 10 cases
	Mastoiditis: 1 case (case 3)
	Cerebral and cerebellar atrophy: 1 case (case 4)
	Right frontal and parietal hyperintense lesions in T2-weighted images: 1 case (case 5)
	Left orbital hemorrhagic collection and thickening of right bulbus posterior wall: 1 case (case 8)
Lumber magnetic resonance imaging (only for case 5)	Stenosis of lumber canal at lumber 3 level
Electromyography (only for case 5)	Normal

TABLE 4: General characteristics of six human immunodeficiency virus infected patients with neurological involvement.

Case number	Age (years)	Sex	CD4+ T lymphocyte count (cells/mm^3)	Plasma HIV-1 RNA (copies/mL)	Duration of HIV infection (months)
7	28	Male	105	1.000	109
13	70	Male	50	< 50	8
15	34	Female	58	>75.000	85
16	40	Male	78	2.600	96
17	17	Male	166	7.000	22
19	62	Male	174	>75.000	85

TABLE 5: Neurological evaluation of six human immunodeficiency virus infected patients with neurological involvement.

Case number	The results of clinical examinations and diagnostic studies
7	Cerebral tuberculoma, pulmonary tuberculosis
	Extensor plantar response on right (positive Babinski sign)
	No cognitive impairment. MMSE: 59 points (normal)
	Cranial MRI: Left frontal cortical enhancing millimetric lesion
13	Ischemic cerebrovascular disease, zona zoster.
	Intentional tremor
	Moderate impairment of attention, remote memory and short-term memory. MMSE: 47 points
	Cranial MRI: Ischemic gliosis
15	Progressive multifocal leukoencephalopathy, oropharyngeal *Candida* infection. Hyperactivity of deep tendon reflexes, clonus of patella and achilles, coreo-atetoic movements, Hoffmann reflex positive bilaterally, and Babinski sign negative bilaterally
	Severe cognitive impairment in all areas. MMSE: 12 points
	EEG: Superficial sleep. Cranial MRI: Cerebral and cerebellar atrophy, hydrocephaly, and findings of progressive multifocal leukoencephalopathy.
16	Mild AIDS dementia complex (Stage 1), mononeuropathy multiplex, oropharyn-geal *Candida* infection.
	Numbness of right foot, and right carpal syndrome
	Mild impairment of frontal lobe function tests, moderate impairment of remote memory, and severe impairment of attention and short-term memory. MMSE: 38 points
	EMG: Mononeuropathy multiplex. Cranial MRI: Left frontal 1 cm lesion deep within the white matter which is hypointense in T1- and hyperintense T2- weighted images
17	Subclinical AIDS dementia complex (Stage 0.5).
	Hypoactivity of deep tendon reflexes
	MMSE: 58 points
	EMG: Normal. Cranial MRI: Normal
19	Severe AIDS dementia complex (Stage 3), distal sensory polyneuropathy, zona zoster, pulmonary tuberculosis.
	Hypoestesia and dystrophic changes in the feet, negative Achilles reflex, truncal ataxia, hypoactivity of deep tendon reflexes, and incontinence
	Mild impairment of remote and short-term memory and moderate impairment of frontal lobe function tests. MMSE: 53 points
	EMG: Could not be tolerated. Cranial MRI: Cerebral and cerebellar atrophy, and hydrocephaly

MRI: Magnetic resonance imaging. EEG: Electroencephalography. EMG: Electromyography. MMSE: Mini Mental State Examination.

impairment compared to those without. No difference was found between the two groups with respect to age, concurrent diseases and duration of HIV infection. Sub-analysis of the patients with ADC and the comparison of results with those of patients with no neurological involvement also revealed similar results. The results were shown in Table 6.

DISCUSSION

Although some studies[6,7] reported low frequencies of (25.6-29.93%) neurological involvement in HIV

TABLE 6: Statistical comparison of human immunodeficiency virus infected patients with neurological involvement and patients with AIDS dementia complex (ADC) as neurological involvement with patients with no neurological involvement.

Parameter	Patients with neurological involvement (n= 6) Patients without neurological involvement (n= 14) Statistical comparison*	Patients with AIDS dementia complex (n= 3) Patients without neurological involvement (n= 14) Statistical comparison*
Duration of HIV infection (months)	8-109 (67.50 ± 41.85)	22-96 (67.67 ± 39.93)
	4-73 (31.14 ± 19.66)	4-73 (31.14 ± 19.66)
	p= 0.099	p= 0.130
CD4+ T lymphocyte count (cells/mm^3)	50-174 (105.17± 53.75)	78-174 (139 ± 53.27)
	65-1.592 (502 ± 400.85)	65-1.592 (502 ± 400.85)
	p= 0.003*	p= 0.044*
Age (years)	17-70 (41.83 ± 20.36)	17-62 (39.67 ± 22.50)
	24-47 (35.07 ± 6.77)	24-47 (35.07 ± 6.77)
	p= 0.620	p= 0.614
Number of patients adherent to highly active antiretroviral therapy	1 case	No case
	11 cases	11 cases
	p= 0.018*	p= 0.029*
Number of patients with co-existing diseases	5 cases	2 cases
	4 cases	4 cases
	p= 0.050	p= 0.515

*Statistically significant if $p < 0.05$.

infected patients, during the course of the infection, up to 30-50% of patients have neurological diseases.[1] Usually the neurological involvement is in the late stages of HIV infection, but 10-50.3% of the patients were reported to present initially with neurological complaints.[1,8] The higher ratio in the second study,[8] which was a retrospective review of 149 HIV-infected AIDS patients, could be attributed to the specialty of the hospital, which was a referral hospital for neurological diseases. Thus, careful and detailed history of patients admitted to neurology clinics, to question the presence of possible risky behaviors for HIV transmission, and anti-HIV testing of the suspected cases would help to diagnose HIV infected patients. In the study presented here, ratios of neurological involvement (30%) and initial presentations with neurological complaints (15%) were similar to the results of earlier studies, as well as the low CD4+ T lymphocyte count of the patients. The mean CD4+ T lymphocyte count of the patients with neurological involvement was reported to be 89 cells/mm^3.[6]

Similar to the variations in frequency of neurological involvement, profiles of neurological conditions also vary between studies.[8] A study[9] from the United States reported ADC in 49.2% of patients with neurological involvement. However, in another study[8] from Mexico, opportunistic infections of the central nervous system (CNS) were reported in 70% of the patients and ADC was reported only in 8.7%. Opportunistic infections also show variations from region to region. In a study[8] from Mexico, CNS toxoplasmosis, cryptococcal meningitis, and CNS tuberculosis were reported in 32.2%, 20.1% and 8.7% of the patients, respectively. In a study[6] from India, however, meningitis was the most frequent CNS infection (39.4%). In one study[9] comparing patients from Mexico City (n= 120) and Houston-Texas (n= 500), intracranial tuberculomas were detected only in the Mexican population (10%). The study commented that the different findings in the Mexican population were likely to reflect afflictions common to developing countries, which is a high pre-

valence of tuberculosis. In the reports of the Turkish Ministry of Health,[10] tuberculosis rates are also high in Turkey and thus, more patients with HIV infection and intracranial tuberculosis might be expected in the future. Co-infections of HIV and tuberculosis are also reported from Europe. Tuberculosis is not only a problem of developing countries, but also of developed countries. A study[11] from Spain also emphasized that in patients with AIDS and proven intracranial tuberculosis (n= 35), more than 90% were intravenous drug abusers and in two thirds of the patients tuberculosis was the first manifestation of AIDS. In the study presented here, three of the 20 cases had active pulmonary tuberculosis and 1 patient had additional intracranial tuberculoma. Similar to the Spanish study,[11] most (two thirds) of the patients with tuberculosis were intravenous drug abusers. Three additional cases reported a history of tuberculosis following HIV diagnosis.

The peripheral nervous system is also affected in HIV infection. Neuropathies such as DSP, inflammatory demyelinating polyneuropathy, progressive polyradiculopathy and mononeuropathy multiplex are other neurological complications that may develop in HIV infected patients. Distal sensory polyneuropathy is the most common form of neuropathy in HIV infection and parallel to declining CD4+ T lymphocyte counts increases in its incidence have been reported. It may develop in up to 35% of AIDS patients.[3] In one study,[7] of the 481 neurological events in 1.527 HIV infected patients, one third were related to neuropathies.

Frequency of cerebrovascular diseases in HIV infection also shows variations. In one study,[12] cerebral infarction was reported in 18% of 71 AIDS patients, and the most common area affected was the basal ganglia (68%). In another study,[8] however, frequency was much lower (5.4%).

The frequency and the spectrum of neurological diseases in HIV infected patients in Turkey are unknown. In the Turkish medical literature, published case reports were the patients with opportunistic infections of the CNS including six cases of cryptococcal meningitis,[13-15] 3 cases of PML,[16-18] 2 cases of pneumococcal meningitis,[19] and 1 case of CNS toxoplasmosis.[20] In the study presented here, the most common neurological disease was ADC (50%), followed by opportunistic infections of the CNS (33%), neuropathies (33%), and cerebrovascular disease (17%). Two patients had more than one neurological disease. Depending on the severity and manifestations, ADC can be a devastating complication of HIV infected patients and impairs the quality of life. Thus, a patient with ADC would most likely need further psychosocial support in the future. In addition, the likelihood of unemployment due to disabilities as well as increased costs of self-care and medical care, would result in an increase in the overall cost.

Although ADC is among the common neurological complications,[1,3] the wide range observed of its frequency (8.7-49%)[8,9] might be associated with a number of factors. First, the diagnosis of ADC is difficult due to the lack of specific studies and the only way to diagnose the condition is to exclude other causes.[1,3] Studies are still run to assess cognitive impairment in HIV-associated dementia. MMSE test, mental alternation test (MAT), modified HIV dementia scale (M-HDS), and Grooved Pegboard (GP) are used to identify patients with HIV-associated dementia.[21-23] Although MMSE test is reported to be inadequate to diagnose patients with early dementia, it is still used frequently because it is simple, time-saving and standardized.[24] Results of neuroimaging studies, also, are not specific for the diagnosis of ADC. Cranial MRI in ADC may show subcortical atrophy more pronounced than that of cortical, which is not proportionate to the degree of dementia, and additionally may demonstrate multiple hyperintense signals in T2-weighted images, which are nonenhancing, ill demarcated, and localized bilaterally in the subcortical white matter. In dementia, MRI is suggested to be superior to computed tomography scanning.[1] In the study presented here, while in 2 cases with ADC, cranial MRI findings were consistent with ADC, in 1 case cranial MRI was normal. Thus, in the presence of normal neuroimaging results, diagnosis of ADC should not be excluded before full evaluating of the patient.

Periodical assessment of HIV infected patients for the presence ADC should be considered

since its incidence may increase with time. In a study[25] that followed-up 203 patients for a median of 20.7 months, HIV associated dementia was detected in 74 (36%) patients who reached the endpoint of the study. The cumulative incidence of HIV-associated dementia was 20% at 1 year and 33% at 2 years.

Another major issue in the assessment of patients for ADC is the differential diagnosis of ADC and depression. In HIV infected patients, many psychiatric syndromes may develop such as adaptation disorders, depressive disorders, anxiety disorders, personality disorders, bipolar disorder, sleep disorder, alcohol and drug abuse, delirium, dementia, and psychosis. HIV infection, opportunistic infections, antiretroviral drugs, and psychosocial stress factors can induce psychiatric morbidity during the course of the infection.[26] The most common behavioral symptoms in ADC are apathy and social withdrawal, which are often misdiagnosed as depression.[3] In the study presented here, cognitive impairment was a consequence of depression in 2 cases. Because depression can be specifically treated, its accurate and timely diagnosis is important.

In conclusion, although the nervous system may be involved in every stage of HIV infection, all patients with neurological involvement in the presented study were in the advanced stages of HIV infection, with a mean CD4+ T lymphocyte count of 105 cells/mm^3. This might be due to delayed seek for medical support by patients or late diagnosis. In addition, most patients with neurological involvement were receiving HAART, but only 1 case was highly compliant with antiretroviral therapy, and all the other 5 cases had detectable plasma HIV-1 RNA levels. Thus, in HIV infected patients, every effort should be made to maintain compliance to therapy. On the other hand, in this study, pathologic findings on cranial magnetic resonance imaging and presence of impairment in cognitive evaluation were also present in patients without neurological involvement. Hence, careful evaluation of the patients for the diagnosis and periodical assessment for early detection of a neurological disease is important.

Longer survival with more effective treatment regimens for HIV infection and opportunistic diseases may result with an increase in the prevalence of neurological involvement in the future. According to the Turkish Ministry of Health, the cumulative number of HIV infected patients in Turkey is 2.254 as of December 2005 (personal communication). However, the actual number is predicted to be much higher due to the likelihood of underreporting. Studies on neurological involvement in HIV infected patients in Turkey are lacking. Diagnosis and reporting of neurological diseases in HIV infected patients are the first steps to collect data for future studies that would determine the frequency and spectrum of neurological diseases in Turkey to aid health authorities in planning future policies and to present results for clinical use. This study was run to draw the attention to this issue.

Acknowledgement

We thank Emel Tümbay, MD and Hatice Uluer for their contributions in the review of the text for English and the statistical analysis, respectively.

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