Nationwide Survey of Neurologic Manifestations of Acquired Immunodeficiency Syndrome in Japan

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To study the epidemiology of the neurologic manifestations of human immunodeficiency virus (HIV)-1 infection in Japan, we conducted two nationwide surveys. Of 1854 HIV-1 carriers, 578 had acquired immunodeficiency syndrome (AIDS) and 166 (28.7% of AIDS patients) had neurologic manifestations including HIV dementia (11.8%), myelopathy (3.6%) and peripheral neuropathy (2.6%). The incidence of neurologic manifestations in patients with HIV-1 infection through blood products was about 60% of that in patients with HIV-1 infection through sex or unknown routes. This nationwide survey showed that the incidence of neurologic manifestations in AIDS patients in Japan was consistent with that in other countries. (Internal Medicine 36: 175–178, 1997)

Key words: acquired immunodeficiency syndrome (AIDS), dementia, myelopathy, human immunodeficiency virus (HIV)-1, epidemiology

Introduction

Human immunodeficiency virus type 1 (HIV-1) infection has gradually become endemic in Japan since 1985 (1). In April 1996, the Acquired Immunodeficiency Syndrome (AIDS) Surveillance Committee of the Ministry of Health and Welfare of Japan reported that cumulative numbers of HIV-1 carriers, patients with AIDS and deceased AIDS patients in Japan were 3642, 1140 and 749, respectively. Opportunistic infections and neurologic manifestations are common complications in HIV-1 infection. Epidemiological studies revealed that neurologic manifestations such as HIV dementia, vascular myelopathy and neuropathy were present in 26% to 50% of patients with HIV-1 infection (2, 3). Of the neurologic manifestations, HIV dementia was observed in 7.3% to 15% of patients with AIDS (3–8). Case reports of neurologic manifestations caused by HIV-1 infection have increased in Japan with increasing numbers of HIV-1 carriers and AIDS patients (9–15). However, no nationwide surveys focusing on the neurologic manifestations of HIV-1 infection have been conducted in Japan. We performed a nationwide survey of the neurologic manifestations of HIV-1 infection in Japan, and found that about 30% of Japanese AIDS patients have neurologic manifestations.

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Methods

Two nationwide surveys were conducted. In the first stage of the survey from January to March 1994, we mailed survey forms to 1,675 institutions including all university and national hospitals throughout Japan. The survey forms requested information on the number of HIV-1 carriers, patients with AIDS, patients with neurologic manifestations suspected to be caused by HIV-1 infection and types of the neurologic manifestations.

In the second stage of the survey in April 1995, we mailed a more detailed survey form to 72 institutions that had reported patients with neurologic manifestations caused by HIV-1 infection. The second survey form requested the following information regarding each patient with neurologic manifestations; birth date, sex, age, age at time of HIV-1 infection, age at onset of AIDS, route of HIV-1 infection, neurological findings, blood cell counts, CD4, CD8, brain computed tomography (CT) and magnetic resonance imaging (MRI) findings, cerebrospinal fluid examination, and peripheral nerve conduction study. In addition to this detailed information of the patients, we requested cumulative numbers of HIV-1 carriers, patients with AIDS, patients with neurologic manifestations caused by HIV-1 infection and types of the neurologic manifestations classified according to route of HIV-1 infection.

Diagnosis of AIDS and HIV-1-associated neurologic mani-

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festations was made based on the 1993 revised center for disease control (CDC) classification system for HIV infection and expanded surveillance case definition for AIDS (16) and the Ministry of Health and Welfare of Japan surveillance case definition for AIDS (17).

Results

In the first nationwide survey, 1,675 institutions were contacted and 1,075 (64.2%) replied (Table 1). Of the 1,854 individuals with HIV-1 infection, 578 were diagnosed as having AIDS. Of these patients, 166 patients (28.7% of 578 AIDS patients on assumption that the neurologic manifestations were associated with AIDS) had neurologic manifestations caused by HIV-1 infection, including 68 patients (11.8%) with HIV dementia, 21 patients with myelopathy (3.6%), 15 patients with peripheral neuropathy (2.6%), 12 patients with toxoplasmosis of the brain (2.1%), and 9 patients with progressive multifocal leukoencephalopathy (1.6%) (Table 2).

In the second nationwide survey, the 72 institutions that had reported patients with neurologic manifestations were contacted and 34 (47.2%) responded. Of the total of 333 individuals with HIV-1 infection reported by these 34 institutions, 164 were diagnosed as having AIDS. Of the 164 AIDS patients, 107 patients (65.2% of 164 AIDS patients on assumption that these neurologic manifestations were associated with AIDS) had neurologic manifestations. Of 188 patients with hemophilia and HIV-1 infection, 54 had AIDS, and 24 (44.4%) of the AIDS patients had neurologic manifestations. Of 145 patients whose route of infection was sexual transmission, 110 had AIDS and 83 (75.5%) of the AIDS patients had neurologic manifestations (Table 3). Of 107 patients with neurologic manifestations regardless of route of HIV-1 infection, there were 44 patients (26.8% of 164 AIDS patients) with central nervous system opportunistic infection, 39 patients (23.8%) with HIV dementia, 22 patients (13.4%) with peripheral neuropathy, 15 patients (9.1%) with malignant lymphoma, and 8 patients (6.7%) with myelopathy (Table 3).

In the second survey, 56 case reports with detailed neurological findings were obtained. Of these 56 patients, 44 had neurologic manifestations (Table 4). Among these 44 patients, there were 12 patients (21.4%) with HIV dementia, 6 patients (10.7%) with central nervous system opportunistic infection, and 5 patients (8.9%) with peripheral neuropathy (Table 5). Twenty-nine of the 56 patients died and 21 (72.4%) of the deceased patients had transmission of HIV-1 infection through blood products. The interval between HIV infection and death was 5 years in these 29 patients, and that between onset of neurologic manifestations and death was 7.3 months in these patients who showed such symptoms (Table 6). Of the 29 (82.8%) deceased patients, 24 showed neurologic symptoms; disturbance of urination and defecation was observed in 20 patients, gait disturbance in 16 patients, muscle atrophy and weakness in 15 patients, dementia in 12 patients, superficial sensory disturbance in 9, and ataxia in 8.

Table 1. Institutions Which Replied to the First Nationwide Survey of Neurologic Manifestations of HIV-1

Institutions	Replied/Contacted	%
University Hospital	290/377	76.9
Internal Medicine	78/98	79.6
Neurology	28/37	75.7
Pediatrics	76/97	78.4
Gynecology	74/87	85.1
Blood Transfusion		
Medicine	32/54	59.3
Others	2/4	50.0
National Hospital	327/482	67.8
Private Hospital	458/816	56.1
Total	1,075/1,675	64.2

Table 2. Neurologic Manifestations Associated with HIV-1 Infection Reported in the First Nationwide Survey

Diagnosis	Number of Patients	% to AIDS patients*
Patients with HIV-1 infection	1,854	
Patients with AIDS	578	
Patients with neurologic manifestations	166	28.7
HIV dementia	68	11.8
Myelopathy	21	3.6
Neuropathy	15	2.6
Malignant lymphoma	13	2.2
<i>Toxoplasma</i> encephalitis	12	2.1
Progressive multifocal leukoencephalopathy	9	1.6
Encephalitis, unknown origin	7	1.2
<i>Cryptococcus neoformans</i> meningitis	6	1.0
Herpes encephalitis	3	0.5
Myositis	2	0.3
Aseptic meningitis	2	0.3
Cerebral infarction	2	0.3

One each of

M. tuberculosis meningitis, Motor neuron disease, Parkinsonism, Neurosyphilis, Cerebral hemorrhage, Amnesia, Mental confusion, Abducens nerve palsy

Some of the patients had more than two neurologic manifestations.

*The percent is calculated on assumption that these neurologic manifestations were associated with AIDS patients.

Discussion

In this nationwide survey, epidemiological aspects of neurologic manifestations caused by HIV-1 infection in Japan were clarified. The incidence of neurologic manifestations in patients with AIDS in Japan was 28.7% and HIV dementia was present in 11.8% of patients with AIDS. The incidence of

Table 3. Cumulative Numbers of HIV-1 Carriers, Patients with AIDS and Patients with Neurologic Manifestations of HIV-1 Infection Reported by 34 Institutions in the Second Nationwide Survey

	All patients	Patients with sexual transmission of HIV-1*	Patients with HIV-1 infection through blood products
Asymptomatic carrier	148	32	116
AIDS-related complex	21	3	18
AIDS	164	110	54
Patients with neurologic manifestations	107 (65.2%)	83 (75.5%)	24 (44.4%)
Opportunistic infection	44 (26.8)	33 (30.0)	11 (20.4)
HIV dementia	39 (23.8)	28 (25.5)	11 (20.4)
Neuropathy	22 (13.4)	18 (16.4)	4 (7.4)
Malignant lymphoma	15 (9.1)	14 (12.7)	1 (1.9)
Myelopathy	11 (6.7)	7 (6.4)	4 (7.4)
Cerebrovascular disease	8 (4.9)	7 (6.4)	1 (1.9)
Myositis	2 (1.2)	1 (0.9)	1 (1.9)
Parkinsonism	1 (0.6)	1 (0.9)	0 (0.0)
Other neurologic manifestations	15 (9.1)	13 (11.8)	2 (3.7)

(): % to AIDS patients calculated on assumption that these neurologic manifestations were associated with AIDS patients. *: including patients with unknown route of HIV-1 infection. Some of the patients had more than two neurologic manifestations.

Table 4. Summary of 56 Patients Reported by 34 Institutions in the Second Nationwide Survey

Male/Female	50/6
Age	37.6±13.5 (range: 10–70)y.o.
Stage of HIV-1 infection	
Asymptomatic carrier	3
AIDS-related complex	3
AIDS	50
Route of HIV-1 infection:	
Blood products	32
Sexual transmission	22
Unknown	2
Neurologic manifestations	
present	44
absent	11
unknown	1

Table 5. Neurologic Manifestations in 56 Patients Reported by 34 Institutions in the Second Nationwide Survey

HIV dementia	12 (21.4%)
Encephalitis/meningitis	10 (17.9)
<i>Toxoplasma</i>	3 (5.4)
<i>Cryptococcus neoformans</i>	1 (1.8)
Cytomegalovirus	1 (1.8)
Herpes virus	1 (1.8)
Unknown	4 (7.1)
Neuropathy	7 (12.5)
Myelopathy	7 (12.5)
Malignant lymphoma	2 (3.6)
One each of	
Progressive multifocal leukoencephalopathy, Myositis, Cerebral hemorrhage, Cerebral M. tuberculosis, CNS Aspergillosis, Diabetes insipidus, Orthostatic hypotension, Cerebellar abscess.	

CNS: central nervous system. Some of the patients had more than two neurologic manifestations.

neurologic manifestations in patients with AIDS ranged from 26% to 50% in other countries (2, 3), and HIV dementia was detected in 7.3% to 15% of patients with AIDS (3–8). Therefore, the incidence of neurologic manifestations caused by HIV-1 infection in Japan detected in this study was consistent with that in other countries.

The incidence of neurologic manifestations in patients with HIV-1 infection through blood products was lower than that in patients with sexual transmission of HIV-1. This suggests that onset of the neurologic manifestations in patients with HIV-1 infection is modified by factors other than HIV-1 itself. The

prognosis of patients with HIV dementia was poor and they died within 4.5 to 7 months on average after onset of this neurologic symptom (8, 14). Therefore, complication by neurologic manifestations such as HIV dementia in association with progression of immunodeficiency is one of the most important clinical features influencing prognosis of AIDS patients.

Only 47.2% of the institutes polled replied to our second survey forms, and thus our results may incorrectly emphasize

Table 6. Summary of 29 Deceased AIDS Patients Reported from 34 Institutions in the Second Nationwide Survey

Male/Female	27/2
Age:	39.4±15.0 (16–70) y.o.
Route of HIV-1 infection	
Blood products	21
Sexual transmission	7
Unknown	1
Neurologic manifestations	
present	24
absent	5
Interval between	
HIV-1 infection and death	61.3±41.1 (0.5–155) months
onset of AIDS and death	16.1±13.2 (0.5–38) months
onset of neurologic manifestations and death	7.3±7.3 (0.5–30) months
Abnormal brain CT findings	16/19 (84.2%)
Abnormal brain MRI findings	10/11 (90.9%)
CD4/CD8	0.09±0.10 (0.005–0.45)

only some aspects of the clinical features of AIDS patients in Japan. Therefore, it is not possible to draw firm conclusions regarding the epidemiological aspects of neurologic manifestations in Japan solely from the results of this study. More detailed cross-sectional and longitudinal studies will be needed to confirm the epidemiology of neurologic manifestations caused by HIV-1 infection in Japan.

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