Parkinsonian Symptoms as an Initial Manifestation in a Japanese Patient with Acquired Immunodeficiency Syndrome and *Toxoplasma* Infection

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Abstract

We studied a Japanese patient who developed parkinsonian symptoms over 3 months before the diagnosis of acquired immunodeficiency syndrome. Brain MRI showed multiple lesions with mass effect and ring enhancement in the basal ganglia and subcortical white matter suggesting *Toxoplasma* infection. Anti-*Toxoplasma* therapy and highly active antiretroviral therapy for 6 months allowed improvement of parkinsonism, brain MRI findings, and immune system.

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Key words: toxoplasmosis, highly active antiretroviral therapy

Introduction

Neurological complications of acquired immunodeficiency syndrome (AIDS) are often found as symptoms of opportunistic infections in the central nervous system (CNS). Parkinsonian symptoms are relatively rare in patients with AIDS (1–6). According to a nationwide survey of AIDS in Japan, from January to March 1994, only one of 578 AIDS patients had parkinsonism (5). Here, we report a Japanese patient who showed atypical parkinsonism before diagnosis of AIDS, and partially recovered after treatment by anti-*Toxoplasma* therapy and highly active antiretroviral therapy (HAART).

For editorial comment, see p 1006.

Case Report

A 49-year-old Japanese man, who had lived in Kobe, devel-

oped a resting tremor in his left hand in August 1998. He felt difficulty in walking, stiffness from the left shoulder to the lumbar portion, and an occasional resting tremor in the right hand by the middle of September 1998. As his symptoms progressed, he returned home to Kumamoto Prefecture in November 1998. He was diagnosed with atypical parkinsonism due to findings of downward gaze palsy and hyperreflexia of the lower extremities and was referred to our institution.

He was admitted to our hospital on November 25. Neurological examination revealed a mask-like face, moderate limitation of downward gaze, and monotonous speech. The upward and horizontal gaze was unimpaired. His pursuit eye movement was saccadic. There was a resting and postural tremor (pill-rolling) in the left hand. Left-sided predominant moderate rigidity was found in the limbs. Rigidity in the left elbow and wrist was cogwheel in character. He showed bradykinesia and typical fixed posture on standing. Postural instability was also observed. His gait was in small shuffling steps with initial hesitation and decreased arm swings. Muscle strength, sensation and cerebellar function were normal. He exhibited hyperalgesia in the plantar aspect of both feet. Tendon reflexes in the lower limbs were moderately hyperactive, although plantar reflexes were flexor. There were no dysautonomic findings such as orthostatic hypotension or sphincter disturbances.

Chest X-P and electrocardiogram were normal. Laboratory findings included a white blood cell (WBC) count of 6,200/ μ l, anemia (Hb 7.8 mg/dl) and a platelet count of 244,000/ μ l. Serum ceruloplasmin, copper and manganese levels were normal. CD4⁺/CD8⁺ cell ratio was 0.20 with a CD4⁺ cell level of 150/ μ l. He was found to be HIV positive by PA, ELISA and Western blot analysis. Copy numbers of HIV-RNA were 270,000/ml. Titer of *Toxoplasma gondii* (TG) IgG was 1/530 and no specific IgM was detected. A serologic test for syphilis (STS) was positive and the titer of the *Treponema pallidum* hemagglutinin (TPHA) test was 1/10,240. Cerebrospinal fluid (CSF) examination showed 6 WBC/ μ l (100% lymphocytes),

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glucose 24 mg/dl and protein 35.5 mg/ml. In CSF, C-reactive protein (CRP) and STS were negative, and the titer of the TPHA test was 1/128. The concentration of homovanillic acid (HVA) in CSF had decreased to 7.1 ng/ml (normal range; 22.4–71.6

ng/ml). SPECT study with ^{99m}Tc -ECD showed normal perfusion in the brain. Electroencephalogram was normal. Nerve conduction studies of his left posterior tibial nerve, deep peroneal nerve and sural nerve were normal. Brain MRI on No-

Figure 1. Brain MRI. Axial T2-weighted images on December 15 showing high intensity signal in the right lenticular nucleus (A) and the subcortical white matter of the left parietal lobe (B). Axial T2-weighted images on May 7 showing disappearance of high intensity signal in the right lenticular nucleus (C) and a size reduction of the high intensity area in the subcortical white matter of the left parietal lobe (D).

vember 27 showed high intensity signal on the T2-weighted image in the subcortex of the left parietal lobe.

Levodopa/carbidopa was started on December 3 and titrated up to levodopa 300 mg/day, resulting in slightly improved hand movement. The patient showed symptoms of confusion such as drowsiness, irritability and emotional lability since December 9. As he was found to be HIV positive, he received antiretroviral therapy (zidovudine 400 mg/day, lamivudine 300 mg/day) and anti-*Toxoplasma* therapy (clindamycin 600 mg/day for 64 days, pyrimethamine 25 mg/day). Piperacillin sodium (4 g/day, IV) was also started for syphilis for 2 days followed by amoxicillin 750 mg/day for 3 months. A repeat MRI on December 15 showed multiple lesions with edema in the subcortical white matter of the bilateral parietal region and right lenticular nucleus, some of which were ring-enhanced by gadolinium (Fig. 1A and B). CSF examination on December 15 showed 16 WBC/ μ l (96% lymphocytes), glucose 37 mg/ml and protein 58.9 mg/ml. PCR test for tuberculosis and JC virus in CSF was negative. Titer of TG IgG in CSF was also negative. Copy numbers of HIV-RNA in CSF were 180,000/ml.

His confusion diminished and his consciousness gradually became clearer. Two inhibitors of HIV protease (ritonavir 800 mg/day, saquinavir 1,600 mg/day) were added on December 25. CD4⁺ cell level was 281/ μ l and copy numbers of HIV-RNA were 1,600/ml on January 8, 1999. A follow-up MRI on February 16 revealed a reduction in the size of the lesions and surrounding edema. His parkinsonian symptoms showed moderate improvement, and the downward gaze limitation disappeared. He was discharged on March 17.

HAART and anti-*Toxoplasma* therapy (pyrimethamine 25 mg/day) have been continued. CD4⁺/CD8⁺ cell ratio was 0.79 with a CD4⁺ cell level of 232/ μ l, and copy numbers of HIV-RNA were under detection (<400 copies) on May 7. A follow-up MRI on May 7 showed a small lesion without edema in the subcortical white matter of the left parietal lobe (Fig. 1D). Neurological examination on July 1 revealed a resting pill-rolling tremor in the left hand, mild cogwheel rigidity and slowness in the left upper extremity, and mild lead pipe rigidity and

hyperreflexia in the lower extremities. The gait was still in small steps, but the frozen gait and postural instability had disappeared.

Discussion

Our patient developed parkinsonian symptoms over 3 months before the diagnosis of AIDS. He showed typical features of Parkinson's disease such as cogwheel rigidity, a pill-rolling resting tremor, bradykinesia, and gait disturbance. However, his clinical course was faster than the usual course of Parkinson's disease, and downward gaze palsy and hyperreflexia in the extremities were recognized. As he showed syphilis infection, HIV infection was tested for, and found to be positive. Brain MRI on December 15 showed multiple lesions with surrounding edema and ring enhancement suggesting *Toxoplasma* infection (Fig. 1A and B). Cerebral toxoplasmosis is the most common cause of mass lesions in the brain of AIDS patients characterized by enhanced lesions with mass effect usually involving the basal ganglia (6, 7). He was also seropositive for TG IgG antibodies in the blood. TG IgG in CSF was negative but did not negate the diagnosis of *Toxoplasma* infection as one-third of patients with cerebral toxoplasmosis exhibit negative CSF (6). Progressive multifocal leukoencephalopathy (PML), malignant lymphoma, and cerebral gumma also had to be considered as differential diagnoses. However, the absence of JC virus in CSF and the mass effect of the lesion did not support the diagnosis of PML. Malignant lymphoma does not respond to drug therapy and cerebral gummas usually arise from dura or pia mater (8).

Movement disorders are relatively rare complications in AIDS patients (1). Most described are hyperkinetic movements, and parkinsonism is only described in a few reports (1–4). *Toxoplasma* infection and cerebral Whipple's disease have been described as causes of parkinsonism in opportunistic infections of AIDS (1–3). The present patient showed bilateral parkinsonism and confusion which were probably due to cerebral toxoplasmosis. Two cases of parkinsonism among AIDS pa-

Table 1. Parkinsonism due to Cerebral Toxoplasmosis in Patients with AIDS

Case	Neurological symptoms & signs	CT or MRI	Treatment & outcome	Reference
1. 66 y female	Bilateral parkinsonism, right-sided pyramidal signs	Two enhancing lesions in the anterior limb of both internal capsules on CT	Pyrimethamine/sulfadiazine, died	Carrazana et al (2)
2. 28 y male	Right-sided parkinsonism, transient right-sided pyramidal signs	Enhancing lesion in the left lenticular nucleus on CT	Pyrimethamine/cotrimoxazole, improved	Noël et al (3)
3. 49 y male	Bilateral parkinsonism, downward gaze palsy	Enhancing lesion in the right lenticular nucleus on MRI	Pyrimethamine/clindamycin, HAART, improved	Present study

tients have been reported in relation to *Toxoplasma* infections (Table 1). Both cases exhibited parkinsonism plus pyramidal tract signs and enhancing lesions in the basal ganglia on brain CT. In the present case brain MRI showed high intensity signals in the right lenticular nucleus on T2-weighted images which probably caused predominantly left-sided parkinsonism (Fig. 1A). The limited clinical response to levodopa may be explained by the direct destruction of postsynaptic dopaminergic structures. HVA in CSF was significantly decreased indicating dopamine depletion in the dopaminergic nigrostriatal system. The patient also showed downward gaze palsy. A *toxoplasma* abscess not seen on MRI might involve the dopaminergic nigrostriatal pathway and the vertical gaze center in the mid-brain. We cannot deny that HIV infection might give rise to parkinsonism and downward gaze palsy. Recently Mirsattari et al (9) described AIDS patients with parkinsonism in which no obvious cause other than the HIV infection was identified. They speculated that HIV infection itself may cause parkinsonism.

His manifestations, brain MRI, and laboratory findings responded to HAART and anti-*Toxoplasma* therapy over 6 months. His parkinsonian symptoms partially improved. A follow-up MRI demonstrated size reductions or disappearances of the multiple lesions in the brain (Fig. 1C and D). The numbers of CD4⁺ increased to 232/ μ l. Cimino et al (7), in 1991 before the introduction of HAART, described that one-third of patients with cerebral toxoplasmosis and HIV infection did not respond to anti-*Toxoplasma* therapy. HAART may have improved the efficacy of anti-*Toxoplasma* therapy through immune system recovery as it has been associated with dramatic decreases of mortality in HIV patients (10, 11). Recognizing movement disorders in early AIDS patients may be important for diagnosis and treatment, as it was in the present case.

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