HIV encephalopathy presenting as schizophrenia-like delusions during highly active antiretroviral therapy (HAART) case report

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ABSTRACT
After HAART (highly active antiretroviral therapy), which is a powerful antiviral drug regimen, was introduced into HIV therapy for AIDS patients, AIDS mortality decreased dramatically. The incidence of encephalopathy among AIDS patients was reported to be 10% to 40% in the past, but the introduction of HAART resulted in a decrease in HIV encephalopathy and an increase in mild CNS-related deficits, which affect the quality of life of AIDS patients. We report the case of an AIDS patient who developed schizophrenia-like delusions associated with encephalopathy. Administration of an antipsychotic drug and hypnotics was effective in relieving the symptoms of patients with insomnia, depressed mood, and delusions. Further information on the neuronal mechanism underlying the mental symptoms observed in our patient will be necessary to understand the process of pathogenesis of the encephalopathy and to devise an adequate clinical strategy for treatment.

Keywords: HIV; Encephalopathy; Schizophrenia; HAART; Antipsychotics

1. INTRODUCTION
There have still been few reports regarding HIV encephalopathy in Japan. 1) According to a WHO report, since the 1990s the mean worldwide HIV infection rate of the adult population (15 to 45 years of age) has been in the 0.8% range. 2) Ever since the powerful antiviral therapy consisting of combinations of several anti-HIV drugs, called HAART (highly active antiretroviral therapy), became established, the numbers of persons who have developed AIDS and died has been decreasing. On the other hand, as a result of the advent of HAART, the life span of HIV patients has grown longer, and the number of patients who develop HIV encephalopathy has increased 3, 4, 5) HIV encephalopathy often develops when the CD4 cell count drops below 100/μl, and before HAART therapy was established, it was observed in 10% - 40% of the patients. Now that HAART has been established, the CD4 cell count of many HIV patients is above 200/μl, and HIV encephalopathy has decreased. 6) We report the case of a patient who, despite good control of his HIV infection, progressed to HIV encephalopathy and exhibited a schizophrenia-like hallucinatory delusional state that was associated with it.

2. CASE REPORT

[Patient] A 38-year-old male whose premorbid personality was introverted and stubborn. His elementary, junior high, and high school grades were average.

[Chief complaint] A hallucinatory delusional state.

[Complications] Hypertension.


[Drinking history] None.

[Smoking history] None.

[History of use of psychoactive substances, such as narcotics] None.

[History of the present illness] The second of two children. Growth and development unremarkable. Both parents died while the patient was in high school, and his sister, who was 7 years older, became a parental substitute. After graduating from a vocational-technical school, he found employment at age 20, but after working for a company for 2 years, he was unable to stand the pressure...
of the work, and resigned. He subsequently performed a series of part-time jobs. The patient is homosexual. At age 26, he was diagnosed with HIV infection. In July of the same year, while an inpatient in the internal medicine department of university hospital A in another prefecture for Pneumocystis pneumonia, he attempted suicide because of anxiety about dying. At age 28, he was admitted for cytomegalovirus retinitis in September, but his visual impairment progressed, and he developed insomnia and suicidal ideation. The patient was examined in the psychiatry department of the hospital because he had taken an overdose of a hypnotic agent, and he was diagnosed with reactive depression. His symptoms improved in response to treatment with etizolam 1.5 mg and mianserin 20 mg. Antiviral drug therapy was subsequently instituted in the internal medicine department of the same hospital (zidovudine monotherapy and in combination with didanosine, lamivudine, nelfinavir, etc). At age 29, treatment with a combination of zidovudine 200 mg, lamivudine 300 mg, nelfinavir 2500 mg was started in May. He had stopped working because of the visual impairment, was receiving public assistance, and continued to live alone. At the time his HIV-RNA load was under 50 copies per ml, his CD4 cell count was 700/μl - 1000/μl, his HIV infection was well controlled, and his CD4 cell count was 700/μl - 1000/μl, and thus his HIV infection was also well controlled.

At age 34, a feeling of residual urine developed around November, and the patient became extremely anxious, thinking that it was a symptom caused by progression of the HIV infection. Because he developed a depressed mood, decreased motivation, a reduced appetite, and insomnia in mid-December, he was started on sertraline 25 mg. Living alone later became difficult, and the patient moved in with his sister. At age 38, auditory hallucinations developed in early January. Because such hallucinations and delusions as “A police officer came in a patrol car, and I talked to the police officer” developed in addition to the depression, the dose of sertraline was increased to 50 mg, and risperidone 2 mg, levomeprazine 25 mg, and diazepam 10 mg were added. When the patient subsequently developed dysuria in addition to poor oral intake, he was admitted to our department as an emergency 7 days after the onset of the hallucinations and delusions.

[Mental symptoms on admission] The patient tended to be drowsy. He was able to answer questions by shaking his head, but he spoke very little. There was no disorientation. A delusion that “I will be picked up by the police” and hallucinations whose content was unknown were noted. Oral intake was poor. The patient resisted being examined, and he finally closed his eyes and no longer responded to questions. The findings resembled the catatonic manifestations of schizophrenia.

[Physical findings] Body temperature: 37.4 C, blood pressure: 199/147 mmHg, pulse: 116/min, SpO2: 97% (room air).

[Neurological findings] No nuchal rigidity. Kernig sign present. No limb paralysis. No sensory abnormali-
es. Babinski reflex and Chaddock reflex positive.

[Test findings on admission] MRI of the head: A wide high intensity area was seen in the brain stem, around the anterior horn of the lateral ventricles, and in the subcortical white matter on T2WI.

Cerebrospinal fluid examination: Cell count 27/3 μl, protein 84 mg/dl, Cryptococcus neoformans (-), tubercle bacillus (PCR method) (-), cytomegalovirus antigen (-), JC virus antigen (-), HIV-RNA 9.4 × 10^9 copies.

EEG findings: A low wave occurrence rate and α wave burst suppression pattern were noted.

[Test findings during the subsequent course] EEG findings on hospital day 10:8 - 10 Hz, 30 - 50 V occipital lobe predominant waves were noted.

Blood examination: HIV-RNA load 31000 copies/ml, CD4 cell count 397/μl.

MMSE: 16/22 points (conducted omitting the 3-step command, reading, naming, and writing and constructional praxis, which require visual acuity. Unable to answer two questions, i.e., region and floor of the building, in regard to orientation to place, and one of three questions in regard to recall.) WAIS-R: VIQ 82 (because of the visual impairment, the PIQ test with blocks, symbols, etc., was not performed. The VIQ test alone was performed). HAM-D on hospital day 18:19 points.

Hospital course] A 1500 ml/day i.v. infusion was administered to treat dehydration. Based on his course the patient was concluded to have been overly sedated by the psychotropic drugs, and the oral psychotropic medication was discontinued. On the same day, quetiapine 25 mg was started to treat his mental symptoms, and all of the hallucinations and delusions subsequently resolved. While nursing care was necessary because of the patient’s impaired vision, he had become familiar with the hospital unit and was largely capable of independent living. On hospital day 14 he was examined in the neurology department, and HIV encephalopathy was diagnosed based on a cerebrospinal fluid examination and the imaging findings. No improvement in the dysuria was observed even after the psychotropic drugs were discontinued. Based on the diagnostic images of the brain the dysuria was judged to be a disturbance caused by the HIV encephalopathy lesions, and it was decided to continue the urinary catheterization. Symptoms of depression, such as a decreased motivation, diminished interest, etc., were noted, but on hospital day 15 the patient’s score on the HAM-D was 19 points, and his course was monitored without prescribing any antidepressant medication. There was also a slight improvement in the patient’s response to conversation and his interest in the other person, but he did not recover to his condition prior to the present episode. On hospital day 42 he was discharged to his sister’s home.

[Post-discharge course] The patient continued to live with his sister after being discharged from the hospital. He gradually regained his vitality, and his response to conversation also returned to its previous level. His mental symptoms stabilized at quetiapine 25 mg. Because his HIV-RNA load on post-discharge day 36 was high, 130,000 copies/ml, and his CD4 cell count had declined even further to 299/μl, the patient was concerned about a progression of his symptoms, and he wanted to resume HAART. It was concluded that he was capable of taking his medication regularly, and on post-discharge day 54 HAART was restarted. On post-discharge day 82 his HIV-RNA load had decreased to 680 copies/ml, and his CD4 cell count had risen to 678/μl.

3. DISCUSSION

It is generally said that HIV encephalopathy often develops when the CD4 cell count is below 100/μl. Even though our patient’s HIV infection was well controlled by HAART, with an HIV-RNA load under 50 copies/ml and a CD4 cell count of 700 - 1000/μl, he developed HIV encephalopathy and exhibited a hallucinatory delusional state, and the symptoms improved in response to psychotropic drugs without changing the content of the HAART regimen. The hallucinations and delusions did not recur after that, even when the psychotropic medication was stopped, and his HIV infection was well controlled, with an HIV-RNA load of under 50 to 74 copies/ml and a CD4 cell count of 700 - 1000/μl, however, a relapse of the HIV encephalopathy was observed 4 years later, and he once again exhibited signs of hallucinations.
and delusions. Although our patient had a past history of Pneumocystis pneumonia and cytomegalovirus retinitis, he had no clear history of central nervous system infection other than the retinitis. Since both a process of improvement of the consciousness disorder and resolution of the mental symptoms were observed in regard to the patient’s hallucinations and delusions, the course of treatment appeared to be different from that of schizophrenia. In the future it seems that it will be necessary to bear in mind HIV encephalopathy cases such as our own, in which the patient exhibited mental symptoms, including hallucinations and delusions, as a result of a longterm central nervous system disturbance, and examine the patients even when their CD4 cell count is adequate. At age 28, our patient’s CD4 cell count was below 10/μl in September, and he developed cytomegalovirus retinitis as a complication. It was estimated that he had probably contracted the HIV infection more than 20 years previously. After infection in the periphery, HIV rapidly migrates centrally, and it causes behavior disorders, motor disorders, and cognitive dysfunction. Our patient’s mother had schizophrenia, but it is unclear whether that contributed to his vulnerability to hallucinations and delusions.

The powerful antiviral therapy call HAART was introduced in Japan about 10 years ago, and the number of patients who die of HIV infection declined, but at that time there was a very harsh situation in which life and death were governed by whether HAART had been introduced to the AIDS unit. Our patient had been admitted to the internal medicine department of hospital A for Pneumocystis pneumonia 3 years before, but at that time HAART had not been established, and presumably the patient became depressed and planned to commit suicide as a result of anxiety of about dying because of seeing patients around him die day after day and thinking that one day the same would probably happen to him. The patient developed cytomegalovirus retinitis as a complication at precisely that time, and he was one of the first patients to receive the benefits of HAART after it became available in Japan. Some of the drugs used in HAART easily pass through the blood-brain barrier, and others do not. Zidovudine has the highest transfer rate of the drugs used to treat our patient, i.e., zidovudine, lamivudine, and nelfinavir, and it has been reported to be effective against HIV encephalopathy. 7) The fact that only a 200 mg dose of zidovudine, i.e., one third the usual dose, could be used in our patient because of impaired hematopoiesis may have played a role in the development of the HIV encephalopathy.

Before HAART was established, HIV encephalopathy was observed in 10% - 40% of AIDS patients, but at present the proportion has declined to 10.5%. On the other hand, the life span of HIV patients has increased as a result of the advent of HAART, and the number of patients like our own who develop HIV encephalopathy despite receiving HAART has risen, 4) Symptoms of HIV encephalopathy, such as cognitive dysfunction, memory disorders, etc., greatly reduce the QOL (quality of life) of patients with HIV infection. When, as in our own patient, a long time has passed after being infected, efforts at early detection and prevention of progression of HIV encephalopathy by means of the HIV Dementia Scale and even more precise psychological tests, 8) and quantitative determinations of viral load in cerebrospinal fluid and other substances that serve as markers, 9) seem necessary, even in cases that have been well controlled by HAART.

4. CONCLUSIONS

HIV testing of schizophrenia patients is rare in Japan. As in our own patient, if there is no advance information in relation to HIV, there is a strong possibility of HIV encephalopathy not being detected or taking too long to diagnose. Even though it is rare, it is necessary to reconsider including HIV encephalopathy in the differential diagnosis of schizophrenia patients in routine clinical practice.

REFERENCES