

Association of AIDS and Bipolar Mania with Rapid Progression to Dementia and Death

Chin-Yi Yang, Tung-Ping Su^{1,5*}, Wing-Wai Wong^{2,5}, Wan-Yuo Guo^{3,5}, Yiet-Ling Su⁴

Division of Psychiatry, Ton Yen General Hospital, Departments of ¹Psychiatry, ²Internal Medicine, ³Radiology, and ⁴Nursing, Taipei Veterans General Hospital, and ⁵National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

Neuropsychiatric complications of human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS) may present clinically as acute or chronic organic brain syndrome, or mimic functional psychiatric diseases. Among such psychiatric diseases, mania tends to occur with increased frequency after the onset of AIDS. We report a case in which manic manifestations were noted before the diagnosis of AIDS. The patient had no past or family history of mood disorders, but had risk factors for HIV infection. He had a rapid downhill course from initial manic symptoms to depression, dementia and then death within 10 months. Such rapid cognitive deterioration into AIDS dementia after mania is consistent with previous reports. Cases like this will become more common with spread of the AIDS pandemic in Asian regions, including Taiwan. Clinicians should be mindful of HIV infection/AIDS as a differential diagnosis in patients with manic episodes and risk factors for HIV infection. [*J Chin Med Assoc* 2005;68(2):92-95]

Key Words: AIDS (acquired immune deficiency syndrome), bipolar mania, HIV (human immunodeficiency virus) infection

Introduction

Acquired immune deficiency syndrome (AIDS) is a disease with various clinical manifestations that affects the immune system and the entire human organism. Central nervous system (CNS)-related manifestations of human immunodeficiency virus (HIV) infection include cognitive impairment, psychotic disorders, mood disorders, CNS opportunistic infections, and neoplasms.¹⁻³ Some opportunistic infections and neoplasms are becoming less common because of the widespread use of highly active antiretroviral therapy (HAART).^{4,5} Conversely, psychiatric disorders related to HIV infection are becoming increasingly recognized. Kilbourne et al surveyed psychiatric comorbidity in 881 HIV-infected veterans and found 46% with significant depressive symptoms, 21% with at-risk drinking, 32% with anxiety, 4% with mania, 4% with schizophrenia, and 11% with cognitive impairment.⁵ Patients with HIV infection or AIDS now live longer

because of treatment advances, but this presents a longer period for psychiatric symptoms to develop. Mental disturbances may influence treatment compliance, quality of life, and risk behaviors for contracting AIDS.⁶ In addition, patients might seek help for psychiatric complaints earlier than for physical distress, i.e. before the diagnosis of AIDS is made.^{7,8} We report a case in which bipolar manifestations were noted before the diagnosis of AIDS.

Case Report

A 37-year-old, divorced businessman presented to our psychiatric outpatient clinic in September 1999 with a 1-month history of elated mood, decreased need for sleep, ideas of grandeur, racing thoughts, hyperactivity, and hypersexuality. No past history of psychiatric disorders, substance abuse, or mood disorders related to medical problems, was elicited. A family history of

*Correspondence to: Dr. Tung-Ping Su, Department of Psychiatry, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: tpsu@vghtpe.gov.tw • Received: July 15, 2004 • Accepted: October 14, 2004

affective disorders, including bipolar disorder, was also negative. An examination of mental status revealed clear consciousness, with alertness and intact orientation. Other than distractibility, no other significant cognitive deficits were noticed. The patient was irritable, excited, grandiose, hypertalkative, and had flighty ideas. He denied auditory or visual hallucinations, or ideas of persecution or being followed. Concurrent impairment of work, social function, and family life, was also reported. Because of a suspected manic episode of bipolar disorder, the patient was given valproic acid 400 mg twice daily and anxiolytic agents. Lithium 300 mg twice daily was added 2 weeks later due to persistently elevated mood, and the patient's manic symptoms were rapidly controlled. Meanwhile, the patient was also diagnosed with chronic bronchitis, manifesting with long-term dry cough and chest tightness; palliative therapy was given at a chest clinic. The patient also complained of diarrhea and weakness of the lower limbs after lithium administration. In December 1999, he experienced a first episode of depression. Sertraline 50 mg once daily was prescribed along with supportive psychotherapy. His mood was stabilized and depression dissipated, but left hand tremor began to appear in January 2000. In the following 2 months, the patient did not return to our clinic. His family reported that 2 weeks before admission, he gradually developed depression again, with somnolence, memory impairment, and inability to manage his daily life.

On March 26, 2000, the patient was brought to our emergency unit with reported mental confusion, disorientation, unsteady gait, intermittent fever, and nystagmus, for 3 days. Lithium intoxication was initially suspected and then ruled out given plasma lithium and valproic acid levels of 0.35 mmol/L and 19.88 mg/L, respectively. Brain computed tomography (CT) and magnetic resonance imaging (MRI) disclosed numerous nodular lesions of various sizes in both cerebral hemispheres (including frontal and thalamic areas, the right posterior parietal region, the caudate head and lentiform nucleus), the brain stem, and cerebellum. The lesions were associated with perifocal edema and mass effects (Figure 1). The imaging findings suggested diffuse CNS infection with cerebritis and/or abscesses, indicating that he was immunocompromised; this clinical impression was subsequently confirmed by positive results of HIV ELISA and Western blot examination. A medical history relating to risk of HIV infection revealed that the patient had stayed in Africa from 1989–1994. During that period, he had malaria and potential sexual exposure to HIV through a relationship with an African woman.

After admission to the infection unit, the patient's initial HIV viral load was 229,592 copies/mL, his CD4 cell count was 34/mm³, and his T4/T8 cell rate was inverted; *Pneumocystis carinii* pneumonia was suspected from chest X-ray. These findings confirmed the diagnosis of AIDS. The patient was then started on HAART for HIV infection. However, the nature of the diffuse nodular lesions remained undetermined because of the absence of a brain biopsy and negative results of cerebrospinal fluid culture. Because of the clinical impression of CNS infection other than HIV encephalopathy, and with differential diagnoses of cryptococcosis, tuberculosis, toxoplasmosis, multicentric glioma, cytomegalovirus encephalitis, and fungal or parasitic infection, antibiotics were administered and the acute distress stabilized. However, the patient continued to have dementia with frequent myoclonic seizures. A follow-up brain MRI scan after 2 months showed evidence of abscess maturation and regression of perifocal edema and mass effects. The patient's total coma scale score was 8, with no improvement in cognitive function. Although a follow-up brain MRI scan after 4 months showed imaging evidence of improved lesions (Figure 2), and although the HIV viral load decreased to 1,491 copies/mL, the patient died of respiratory failure 10 months after the initial manic episode.

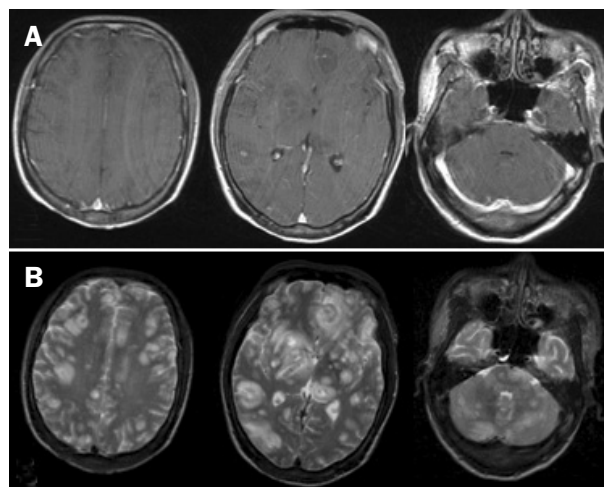


Figure 1. Initial magnetic resonance imaging scan of the brain. (A) Three slices of T1-weighted trans-axial images with contrast-agent injection showing multiple, faint, enhanced nodular lesions of various sizes in both cerebral hemispheres (including frontal and thalamic areas, the right posterior parietal region, and the caudate head and lentiform nucleus), the brain stem, and cerebellum. The cortical sulci were effaced, and the ventricular system squeezed, secondary to mass effects of the lesions. (B) Three slices of T2-weighted trans-axial images, with the same positioning as Figure 1A, and revealing mixed-signal lesions and associated perifocal edema.

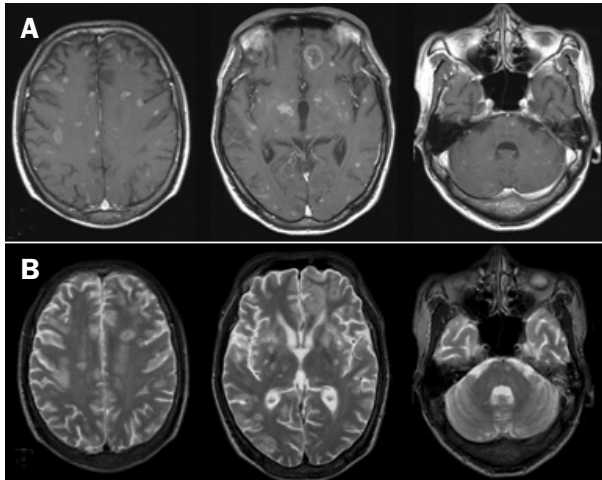


Figure 2. Magnetic resonance imaging scan after 4 months. (A) Three slices of T1-weighted trans-axial images, with similar parameters as in Figure 1A, showing obvious regression of the mass effects after maturation of the abscess. The cortical sulci and ventricular system were normalized. (B) Three slices of T2-weighted trans-axial images, with the same positioning as Figure 2A, revealing conspicuous regression of the lesions and mass effects.

Discussion

In this report, we highlight a case of secondary mania, which appeared to be the first symptom of AIDS, but which, in fact, was the late phase of CNS HIV infection.

Manic syndrome affects approximately 8% of AIDS patients, and generally occurs late in the course of HIV disease.⁹ Lyketsos et al compared groups of patients with HIV infection and mania according to whether their first manic episode occurred when CD4 count was less than 200/mm³ (late-onset mania) or at least 200/mm³ (early-onset mania).¹⁰ The late-onset patients were less likely to have personal or family histories of mood disorder and more likely to have dementia or cognitive slowing.

Previous studies have tried to determine the pathogenesis of HIV-related mania. Firstly, since HIV preferentially affects subcortical gray matter such as the caudate nuclei and cortical white matter, both of which are important to the regulation of mood, manic symptoms might indicate CNS HIV infection.¹¹ Secondly, Dreyer et al reported that purified HIV coat protein, gp 120, increased intraneuronal calcium *in vitro* in a dose-dependent manner.¹² HIV-related mania may be caused by accumulation of intracellular free calcium, which has been implicated in the pathogenesis of bipolar disorder.¹³ Thirdly, el-Mallakh suggested that mania or hypomania appeared to be related to immunosuppression and progression of

HIV disease.¹⁴ Previous reports have also suggested that manic or hypomanic symptoms are indicators of poor outcome in AIDS.^{3,14} However, the underlying mechanism is unclear. Our patient had no previous or family history of mood disorders. He had a rapidly downhill course from mania to depression, dementia, and death within 10 months. Given the above findings, our patient was more likely to have secondary mania, and the clinical course was similar to that in el-Mallakh's report,¹⁴ in which nearly a quarter of patients with AIDS-related mania died within 6 months of the initial psychiatric presentation.

Also consistent with previous studies,¹⁴ the secondary manic syndrome in our case seemed to respond adequately to pharmacotherapy (i.e. valproic acid and lithium). However, patients with AIDS or CNS HIV infection may be more prone to the adverse effects of medication such as delirium, lithium toxicity, and extrapyramidal symptoms.^{6,14} Similarly, our patient experienced adverse effects, such as diarrhea, lower-leg weakness, and hand tremor, even with a small amount of mood stabilizers. These problems, accompanied by chest tightness, were also possibly due to progression of HIV infection. Interestingly, in a 3-year follow-up study, antiretroviral therapy demonstrated protective efficacy against the development of AIDS-related mania by halting HIV penetration into the CNS.¹⁵ Unfortunately, the AIDS diagnosis in our patient was not made until the late stage when HIV infection was established in the CNS and the protective effect of HAART had failed.

The next questions are: can HIV/AIDS be identified when masked by psychiatric symptoms; and can the progression of HIV infection to AIDS be prevented? The answers to these questions are not definitive, particularly in Taiwan, as clinician alertness to the diagnosis of HIV/AIDS is still somewhat lacking. In our case, the important information was not initially discovered in the patient's history. We did not know, until the patient presented with disturbed consciousness, and until AIDS was diagnosed, that the patient had stayed in Africa, had been infected with malaria, and had had a long-term sexual relationship with an African woman. Furthermore, the patient's hypersensitivity to adverse effects, even with low doses of antimanic medications, may also have provided a clue as to some type of CNS infection.

Progressive multifocal leukoencephalopathy (PML) is considered an important differential diagnosis for CNS complications of AIDS in many countries, including Taiwan.¹⁶ The hallmark of PML in the brain is patchy or confluent areas of low attenuation on CT scan, or hyperintensity of T2-weighted images on

MRI scan. These lesions are generally not contrast-enhancing and are not surrounded by edema. They are usually bilateral, but asymmetric, and localized preferentially to the periventricular areas and subcortical white matter.¹⁷ The imaging findings in our case are unlike those in PML. The multiple nodular lesions with perifocal edema suggested the presence of cerebritis and/or abscesses in both cerebral hemispheres, mostly the cortical areas. However, the lesion pathology could not be elicited because the family refused a biopsy of the patient's brain.

In Taiwan, although HIV/AIDS is not as common as in the US, the gradually increasing prevalence should make clinicians alert to the possibility of HIV/AIDS as a differential diagnosis for bipolar disorder. Previous studies have suggested that patients with severe psychiatric illness have increased rates of HIV infection.^{18,19} Cournos and McKinnon reported an overall HIV infection rate of 7.8% among psychiatric patients,¹⁸ compared with an estimated rate of 0.4% in the general US population. High-risk behaviors, especially intravenous drug abuse and unprotected sex, are reported by 20–50% of psychiatric patients, particularly those with schizophrenia or bipolar disorder.¹⁹ Besides early detection of HIV infection, managing psychiatric symptoms is particularly important, since patients may actually spread HIV through impulsivity⁶ or hypersexuality in the manic phase.

Since the HIV/AIDS epidemic in Taiwan has progressed, we report this case to highlight the difficulties in diagnosing AIDS masked by bipolar mania. Clinicians should include HIV infection in the differential diagnosis of patients at high risk of such infection and who present with mania. With earlier diagnosis and HAART, patients may have the opportunity to live longer. Psychiatric intervention can potentially alter the course of HIV infection and improve patient quality of life.

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