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HIV-associated parkinsonism reversed with antiretroviral therapy

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Abstract

Human immunodeficiency virus (HIV) infection can cause variable movement disorders, including parkinsonism. HIV-related parkinsonism usually responds well to highly-active antiretroviral therapy (HAART), suggesting a possible reversible dysfunction of the dopaminergic system. We report the case of a 42-year-old man who presented with rapidly progressive symmetric parkinsonism, cognitive decline, and loss of postural reflex as the initial manifestation of HIV infection. A significant improvement of his parkinsonism after HAART demonstrates a potentially reversible dopaminergic system dysfunction secondary to HIV infection. A normal ^{99m}Tc-TRODAT-1 SPECT image after HAART treatment paralleled the clinical improvement in extrapyramidal symptoms. Early identification of HIV-related parkinsonism, especially in patients with symmetrical akinetic-rigidity and early loss of posture reflex, is important for its potential reversibility with HAART therapy.

INTRODUCTION

Movement disorders, including hemichorea-ballimus, myoclonus, dystonia, tremor, and parkinsonism, are not rare in human immunodeficiency virus (HIV)-associated central nervous system (CNS) complications.[1] Parkinsonism, either isolated or secondary to prior exposure to neuroleptic agents[2,3] or intracerebral opportunistic infections[4-6], occurs in up to 5% of patients with HIV infection. Isolated parkinsonism as a primary initial manifestation of HIV infection has rarely been reported.[7-9]

Whether the nigro-striatal dysfunction in HIV-related parkinsonism is reversible after highly-active antiretroviral therapy (HAART) remains unclear. Single photon emission computed tomography (SPECT) of dopamine transporters with ^{99cm}Tc-TRODA-1 is a valuable and feasible means of assessing the integrity of dopamine neurons. Here, we report a case of HIV infection with parkinsonism as the presenting feature in which extrapyramidal symptoms improved significantly after HAART without dopaminergic drugs. The ^{99m}Tc-TRODAT-1 SPECT image showed intact dopamine transporter uptake in the bilateral basal ganglia.

CASE REPORT

A 42-year-old man presented with a 4-month history of rapidly progressive general slowness, gait unsteadiness, and cognitive decline. Frequent falls developed within 2 months and he became wheelchair-bound. The patient was in a heterosexual relationship and had no history of injection drug use or prior exposure to neuroleptic agents. Neurological examination revealed symmetric parkinsonism features, including mask face, bilateral prominent cogwheel rigidity, bradykinesia, and impaired postural reflex (Video 1). Generalized hyperreflexia with extensor plantar reflex was observed on the right side. The Unified Parkinson's Disease Rating Scale part III (UPDRS-III) score was 66 out of 108. A mental status examination revealed poor attention; little verbal output; frontal releasing signs, including palmomental, grasping, and glabella signs; and bilateral apraxia of the hands. The Mini-mental State Exam (MMSE) score was 9 out of 30. Brain magnetic resonance imaging (MRI) revealed confluent white matter lesions with increased T2 signal involving the subcortical to periventricular area bilaterally and the pontocerebellar tract without contrast enhancement (Figure 1A). The basic blood tests, including liver/renal function, iron profiles, thyroid/parathyroid function, venereal disease research laboratory (VDRL) test, and serum vitamin B12, were all within normal limits. Further investigations revealed a decreased peripheral lymphocyte count, and the test for Wilson's disease was negative. A subsequent HIV test was positive. The patient's CD4 T cell count was 25 cells/mm^3 and HIV viral load was 475,000 copies/mL. The cerebrospinal fluid had

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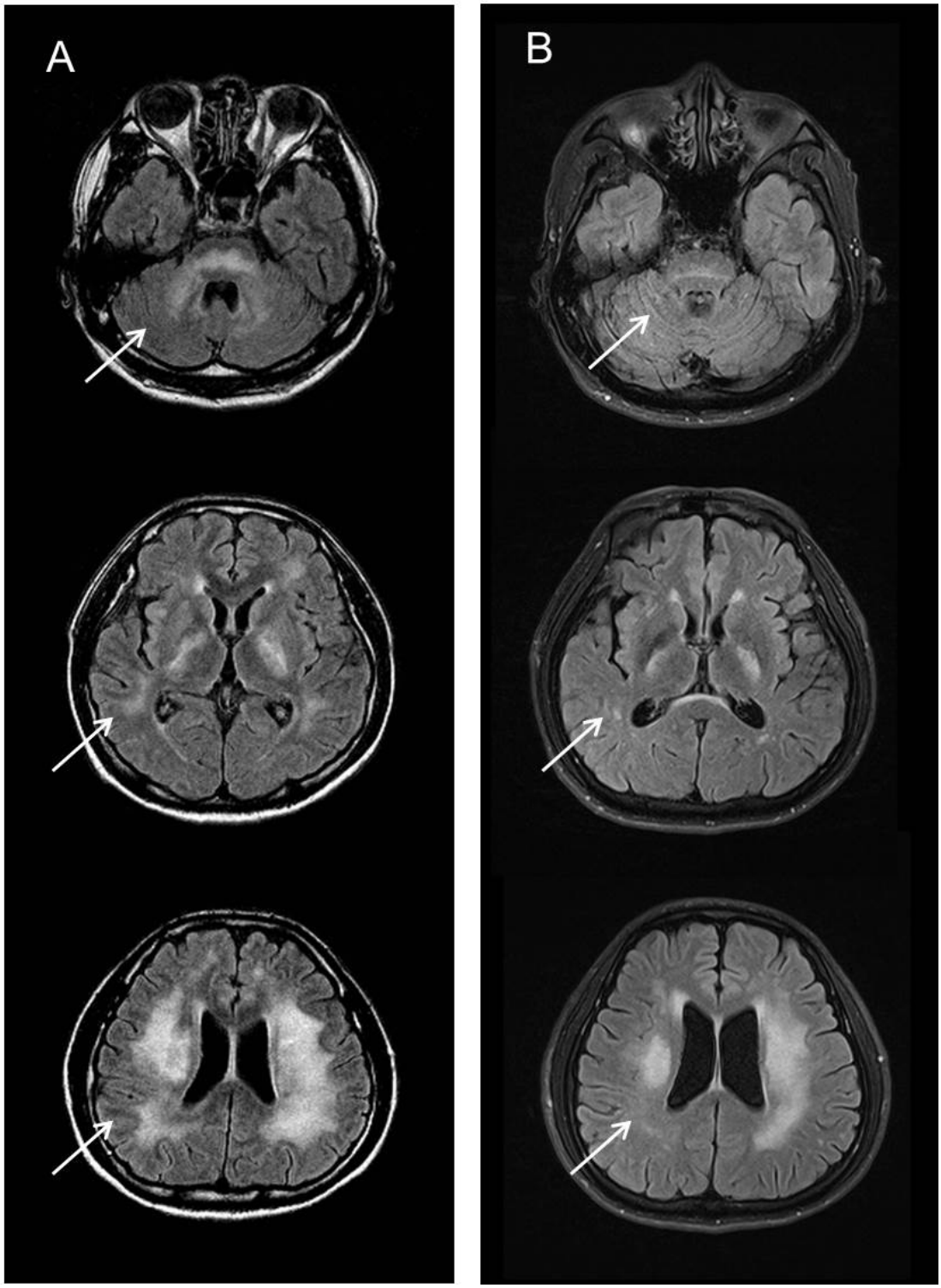

Figure 1. Brain MRI of the patient before and 5 months after initiation of HAART. **(A)** The brain MRI before HAART showed confluent white matter lesions with increased T2 signal involving the subcortical to periventricular area and pontocerebellar tract (arrows). (B) Follow-up brain MRI 5 months after the initiation of HAART showed significantly reduced white matter lesions in the subcortical deep white matter and pontocerebellar tracts (arrows).

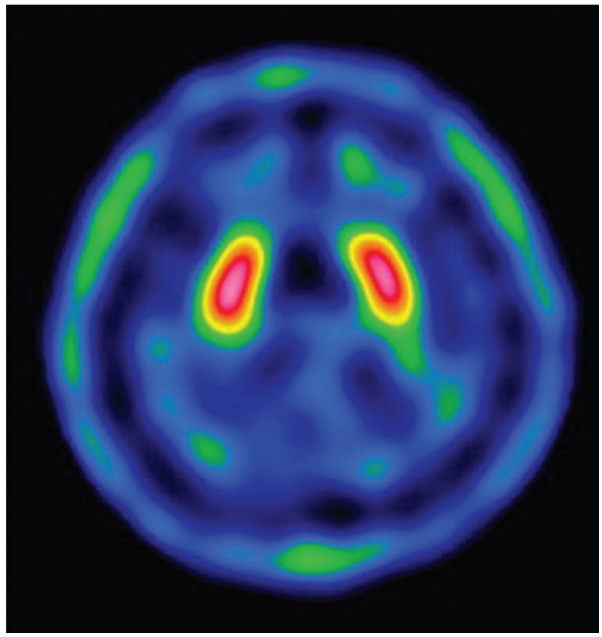

Figure 2. ^{99m}TCTRODAT-1 SPECT scan of the patient 5 months after HAART. The ^{99m}TRODAT-1 SPECT study showed normal dopamine transporter binding in the bilateral basal ganglia 5 months after HAART.

an elevated protein level (102.7 mg/dL) and IgG production (IgG index 0.82) without pleocytosis, with an HIV viral load in the cerebrospinal fluid of 71,000 copies/mL. Polymerase chain reaction (PCR) analysis for JC virus, CMV, and EBV was negative. The patient started to receive HAART treatment (nevirapine 200 mg/day for 10 days, with 400 mg/day thereafter; lamivudine 300 mg/day; and zidovudine 600 mf/day). The patient's CD4 T cell count increased to 199 cells/mm^3 and his serum HIV viral load reduced to 183 copies/mL after 6 months of treatment. His parkinsonism features and imbalanced gait also improved; after 5 months of treatment, the patient's UPDRS-III score reduced to 12 and MMSE improved to 28 (Video 2). A follow-up brain MRI showed reduced white matter lesions in the subcortical deep white matter and pontocerebellar tracts (Figure 1B). Parallel with the clinical improvement, ^{99m}Tc-TRODAT-1 SPECT imaging showed normal dopamine transporter binding in the bilateral basal ganglia (Figure 2). At the most recent follow-up 6 months after onset of initial symptoms, the patient had no obvious bradykinesia or rigidity and he was functionally independent.

DISCUSSION

We reported the case of a 42-year-old male patient with rapid progressive parkinsonism as the initial presentation of HIV infection. Our subject exhibited improvements in both his parkinsonism and cognitive function after 5 months of HAART therapy. As these improvements occurred without the use of dopaminergic agents and paralleled a reduction in the serum HIV viral load and increase in CD4 T-cell count, we attribute these beneficial responses to effective HAART therapy.

Previous case studies have also shown that HIV-related parkinsonism responds well to HAART therapy.[7-9] Hersh *et al*. reported a 37-year-old man whose parkinsonism symptoms resolved after 6 months of HAART treatment with normalization of the serum CD4 count.[8] Kobylecki *et al.* reported another 40-year-old man with a resolution of parkinsonism features after a couple of months of HAART therapy.[7] Jang *et al*. reported a case with progressive supranuclear palsy-like parkinsonism and dementia whose parkinsonism improved with unclear treatment duration of HAART, whereas the dementia kept deteriorating.[9] These cases, along with the clinical improvement observed in our patient, point to a reversible nature of HIV-related parkinsonism.

In addition to the clinical improvement in parkinsonism, a notable feature in our patient is the normal dopamine transporter imaging after HAART therapy. However, a pre-HAART treatment ^{99m}Tc-TRODAT-1 SPECT scan was not available for comparison. Kobylecki *et al.* reported bilaterally reduced putaminal uptake

by dopaminergic transporters using [123I]FP-CIT SPECT in a HIV-related parkinsonism patient before HAART therapy[7], although a follow-up image is not available.

Previous studies have evaluated the dysfunction of dopaminergic neurons in HIV-infected patients using functional imaging. Wang *et al*. demonstrated significantly reduced dopamine transporter uptake in the putamen and ventral striatum in HIV patients with dementia compared to those without dementia.[10] Also, increased neuron loss in the substantia nigra has been described in HIV-infected patients without neurological abnormalities compared to control subjects.[11] The exact mechanism by which dopaminergic neurons are vulnerable to HIV infection is unclear. *In vitro* studies have shown that HIV enters the brain shortly after initial infection when macrophages harboring the retrovirus cross the blood-brain barrier.[12] Direct infection with HIV has been demonstrated in macrophages and microglia, but not neurons. Therefore, the neurotoxicity of HIV has been proposed to come from the indirect effects of infected microglia. An HIV coat protein, envelope glycoprotein 120, could bind to microglia, with the cytokines released by activated microglia to nearby dopaminergic neurons resulting in neurotoxicity.[13,14]

The MRI findings of our patient showed diffuse white matter changes of increased T2 signal involving bilateral subcortical to periventricular area and pontocerebellar tract without contrast enhancement. Previous studies have shown that HIV enters the CNS within days to weeks of infection through "Trojan horse" trafficking of HIV-infected macrophages across the cells of the blood–brain barrier, triggering viral dissemination in the CNS. The clinical neurological deficits usually occur much later after HIV infection, and the dissociation between viral load and observed lesions favors an indirect mechanism for the pathogenesis of HIV-related CNS lesions.[12-14] Typical lesions are present in the white matter and extend to the basal ganglia and cortex with disease progression, but they can also be present in the brainstem, cerebellum, and spinal cord. T2-weighted MRI and fluid attenuation inversion recovery (FLAIR) images usually reveal high signal, isolated, scattered, or confluent lesions without mass effect in the periventricular white matter and centrum semiovale that correspond to demyelination and vacuolations, without enhancement on post-contrast T1 images.[15,16] In agreement with our patient, HAART could result in some regression or stabilization of these CNS findings.[17]

In conclusion, given the potentially reversible nature of HIV-related parkinsonism after optimal HAART therapy, early identification of HIV infection is important. For patients presenting with rapidly progressive parkinsonism, especially with atypical features such as symmetric presentation, early postural instability, and concurrent cognitive decline, HIV infection should be considered.

Video legends

Video 1. http://neurology-asia.org/content/19/2/neuroasia-2014-19(2)-199-v1.wmv Prominent parkinsonism features, including mask face, bilateral akinetic-rigidity, and impaired postural reflex, in the index patient before HAART.

Video 2. http://neurology-asia.org/content/19/2/neuroasia-2014-19(2)-199-v2.wmv Improvement in the index patient's parkinsonism features with only mild mask face after 5 months of HAART.

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DISCLOSURE

Conflicts of interest: None

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