HIV-associated dementia

Prompt response to zidovudine

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In April 2009, a 47-year-old HIV-infected man visited the outpatient clinic with a 4-month history of extreme fatigue. Within 4 weeks, his fatigue progressively worsened, and he developed memory problems. He became apathetic, showed lack of initiative, and developed clumsiness, an unsteady gait, and speech problems.

He had been diagnosed with HIV infection in 2001 and started with combination antiretroviral therapy (cART) in 2002 when his CD4 cell count was $220 \times 10^6/\text{L}$. He developed *Pneumocystis carinii* pneumonia in 2003, and was diagnosed with Crohn disease, Graves disease, and a cutaneous herpes infection. He was treated with lamivudine, lopinavir, ritonavir, tenofovir, mesalazine, loperamide, and temazepam.

On neurologic examination, the patient's blood pressure was 108/68 mm Hg, heart rate 60 beats/min, temperature 37.2°C. He was alert, but extremely bradyphrenic, and had dysarthric speech. He was disorientated in time and place and scored 25 out of 30 on a Mini-Mental State Examination. There were moderate coordination problems with severe gait imbalance and signs of a sensory polyneuropathy of his lower extremities.

Laboratory results showed no signs of infection and normal renal, liver, and thyroid functions. His CD4 cell count was $530 \times 10^6/\text{L}$; the blood HIV load 303 copies/mL. Brain MRI showed extensive symmetrical white matter hyperintensities in the brainstem, cerebellum, and temporal and frontal lobes (figure 1A), basal ganglia (figure 1B), periventricular, and corpus

Figure 1 Axial MRI scan of the brain at presentation: Fluid-attenuated inversion recovery images

At presentation symmetrical hyperintensities in the brainstem, cerebellum, temporal lobes (A), basal ganglia (B), periventricular and corpus callosum (C).

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Figure 2 Axial MRI scan of the brain two months after treatment: Fluid-attenuated inversion recovery images

Two months after zidovudine treatment, there was a significant decrease of white matter abnormalities compared to images at presentation (see figure 1).

callosum (figure 1C). CSF contained 39 cells/ μ L, an elevated protein of 1.97 g/L, and the CSF HIV load was 7,484 copies/mL. CSF was negative for bacteria, *Cryptococcus neoformans*, JC virus, and herpesviruses. Resistance analysis showed no differences in genotype of the blood and CSF viral strain; however, the strain was resistant for protease inhibitors.

A diagnosis of HIV-associated dementia (HAD) was made and zidovudine 300 mg BID was added to the patient's cART. After 5 days, a remarkable improvement was noticed. In the weeks thereafter, his cognitive and motor problems further improved dramatically. His CSF contained 29 cells/ μ L, protein of 1.88 g/L, and his CSF HIV load decreased to 463 copies/mL after 5 days of treatment with zidovudine; the serum HIV load decreased to 89 copies/mL. After 2 months of treatment, brain MRI showed an important decrease of white matter abnormalities (figure 2). He recovered completely. Therefore and based on the viral resistance pattern, his cART was changed to lamivudine, abacavir, zidovudine, raltegravir, and efavirenz.

This is a remarkable case for several reasons. This patient developed HAD after years of a steady course without any change in his cART. The various antiretroviral drugs differ in CNS penetration. For that reason, the CNS penetration effectiveness ranking (CPE) has been introduced.¹ This ranking is a tool to score the CNS penetration of various combinations of drugs. Although there is controversy about its clinical usefulness, most clinicians will try to increase the CPE score of the cART in a patient who develops cognitive impairment. However, addressing the resistance pattern of the breakthrough virus in the CNS should also be a main target for redesigning therapy. Our patient used lopinavir/ritonavir, with a high CPE, and 2 others in his cART with a lower CPE. His HIV strain turned out to be resistant to protease inhibitors (lopinavir/ritonavir), resulting in suboptimal viral suppression in the CNS. Secondly, the MRI abnormalities in our patient were remarkably symmetrical and extensive. Finally, the response to the change in therapy, both clinically and radiologically, was impressive.

There is no gold standard to diagnose HAD. A HIV dementia scale, neuropsychological assessment, brain MRI, and CSF examination should be part of the standard diagnostics when there is a suspicion of HAD. HAD can only be diagnosed when all other (mostly infectious) causes are ruled out. Since the introduction of cART, the incidence of HAD has decreased substantially.² However, physicians should consider HAD in cART-treated HIV-infected patients with cognitive and motor dysfunction, even when systemic immunologic and viral response is sufficient.

Lessons to be learned from this case:

- Suboptimal suppression of HIV replication in the CNS can lead to HAD even in patients who are well suppressed systemically.

- HAD is characterized by symmetrical white matter abnormalities on MRI and detectable levels of HIV load in the CSF, usually several hundred up to tens of thousands of copies of HIV RNA.
- If HAD develops, the CPE score of the cART should be increased, or therapy redesigned based on the results of resistance pattern analysis.
- The response to treatment can occur within a few days to weeks.

REFERENCES

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