Psychosis of dual origin in HIV infection

Viral escape syndrome and autoimmune encephalitis

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Neuropsychiatric disturbances are frequent in HIV infection and may be caused by many conditions, including metabolic abnormalities, opportunistic infections, and immune disorders, among others.¹ The fact that several conditions coexist in patients with HIV is particularly difficult. We describe here a patient with HIV with coexisting evidence of a viral escape syndrome and an antibody-mediated autoimmune encephalitis (against NMDA receptor [NMDAR]).

A 48-year-old woman was admitted in August 2017 for a 6-week history of progressive abnormal behavior (i.e., she pretended to feed nonexistent animals and threw food on the floor) together with an incoherent discourse (“I have to feed the people fighting at the war”) and auditory and visual hallucinations. She progressed to a catatonic state.

She had been diagnosed with HIV infection in 1988 and had been treated for hepatitis C virus with ombitasvir, paritaprevir, ritonavir, and ribavirin until viral eradication in January 2017. During hepatitis C treatment, her usual HIV therapy (efavirenz, tenofovir, and emtricitabine) was reduced to darunavir and ritonavir. She did not receive neuroleptics. She had not had any previous opportunistic infections and was not receiving prophylaxis. She had remained stable with a low viral load on antiretroviral drugs for many years until admission.

She was febrile (38°C) and had consciousness fluctuations. When fully alert, she was catatonic, did not respond to orders, and suddenly would start crying or yelling. Her 4 limbs were rigid, and her muscle reflexes were hyperactive with ankle clonus. On admission, her CD4 count was 628 cells/mm³, and plasma HIV load was 60 copies/mL.

Brain MRI (figure) showed a nonenhancing, moderately expansive corticosubcortical lesion involving the left temporomesial region, parahippocampus, and fusiform gyri, extending to the occipital horns. There was no diffusion restriction, bleeding areas, or increased perfusion. An EEG showed nonspecific diffuse slowing without epileptiform changes.

A spinal tap showed clear CSF with glucose 65 mg/dL (normal, <50 mg/dL), proteins 83 mg/dL (normal <45 mg/dL), 35 lymphocytes/mm³ (normal, up to 5 cells/mm³), increased immunoglobulin G (IgG) index of 5.58 (normal <0.7), and the presence of several IgG oligoclonal bands with a type IV pattern (identical oligoclonal bands in serum and CSF) and immunoglobulin M (IgM) bands with a type III pattern (oligoclonal bands in CSF and serum with additional bands in CSF). HIV load in the CSF was 45,600 copies/mL. A complete microbiologic workup was negative, including CSF aerobic, mycobacterium, and fungal cultures. Serology for syphilis in serum and CSF was negative. PCR on CSF was negative for herpes viruses (HSV1-2, HHV6, HHV8, and cytomegalovirus) and JC virus. Serum antibodies to *Toxoplasma gondii* were not detected.

PRACTICAL IMPLICATIONS

Consider anti-NMDA encephalitis and viral escape syndrome (low HIV load in serum and high in CSF) in patients with HIV with neuropsychiatric disturbances because both require specific therapy measures. Anti-NMDA encephalitis requires immunotherapy; viral escape syndrome requires an antiretroviral regimen. CD8 encephalitis may coexist with viral escape syndrome and may respond to steroids.

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FLAIR MRI showing bilateral hyperintensities on medial temporal lobes predominantly on the left side, involving the amygdala (arrows) and parahippocampal and fusiform gyri (arrowheads, left image). Nodular lesions involving the U-fibers of the occipital and temporal lobe white matter, particularly on the left side (arrowhead, middle image). Widespread involvement of the periventricular white matter of the frontal and parietal lobes, sparing the U-fibers (arrows, right image). There was no brain atrophy, contrast enhancement, or diffusion restriction (not shown). FLAIR = fluid attenuated inversion recovery.

Her antiretroviral HIV therapy was potentiated with tenofovir, emtricitabine, and raltegravir, but her condition worsened with daily fever and she progressed into a coma with severe, diffuse waxy rigidity. Darunavir was added with no effect; it was replaced for nevirapine. Acyclovir, ceftriaxone, and meropenem were added without improvement. On the seventh day of admission, IV methylprednisolone 500 mg was administered daily for 5 days with no response.

CSF showed the presence of antibodies against the NMDAR. Antibodies were determined at the University of Barcelona (Dalmau's laboratory). Studies were comprehensive and included immunohistochemistry with rat brain tissue, and cell-based assays with HEK293 cells expressing NMDAR.^{2,3} The studies were negative in serum and positive in CSF. The antibody titer in CSF was 1:160. The combination of techniques excludes false-positive cases. A panel of other onconeuronal antibodies was negative.

With the suspicion of autoimmune encephalitis, the patient received IV immunoglobulins (0.4 mg/kg daily for 5 days) with a clear response in a few days. Additional therapy with rituximab was not considered, given that her HIV status could have resulted in severe immunosuppression.

A search for ovarian teratoma and occult neoplasia was negative. Five weeks later, she was discharged in her baseline condition on therapy with emtricitabine, tenofovir, nevirapine, and raltegravir.

A follow-up brain MRI performed 7 months later showed the almost complete disappearance of the temporal lobe hyperintensities. The diffuse white matter involvement remained unchanged.

Discussion

The differential diagnosis of progressive neuropsychiatric symptoms in patients with HIV includes toxic and metabolic conditions, vasculitis, opportunistic infections, HIV encephalitis, and neoplasms secondary to immunodeficiency, among others. However, the normal CD4 cell count together with a low HIV load in serum but a disproportionately high CSF load characterizes the HIV escape syndrome, which occurs in patients who are stable on antiretroviral treatment and likely represents a compartmentalization of the virus to the CNS.^{4,5} The MRI findings were also consistent, with diffuse T2 hyperintensities predominantly in the white but also in the gray matter. In patients with this condition, adjusting or increasing the antiretroviral regime to achieve better penetration into the CNS is usually advised. CD8 T-cell encephalitis may be associated with HIV escape syndrome, although symptoms are accompanied by widespread inflammatory changes on brain MRI, and this syndrome usually responds to steroids.⁶ Our patient did not respond. It usually causes a rapidly progressive subacute encephalopathy and likely represents a form of CNS immune reconstitution syndrome.

The high titer of antibodies to NMDAR in CSF together with a temporal lobe lesion on MRI and a clear-cut response to IV immunoglobulins were suggestive of NMDAR autoimmune encephalitis.⁷ Why she did not respond to steroids is unclear. Her underlying diagnosis of HIV made recognition of an autoimmune etiology particularly difficult.⁸

Several aspects deserve further comments in this case. The presence of a combined pathology contributing to clinical symptoms in a patient represents an exception to the Occam's razor rule to be considered in patients with HIV with

neurologic disorders. The combination of an HIV viral escape syndrome with an associated autoimmune encephalitis has been described only once in the literature,⁸ but its recognition is of utmost importance because both are treatable disorders and are easily mistaken for other conditions. Finally, neuronal autoantibodies may be present only in CSF.

The coexistence of several conditions in patients with HIV with neuropsychiatric disturbances should be considered so that patients can be properly treated.

Author contributions

D. Anguizola-Tamayo, J. Bocos-Portillo, L. Pardina-Vilella, A. Rodriguez-Sainz, E. Martínez, M. Gomez Beldarrain, and J.C. Garcia-Monco were involved in writing the manuscript and obtaining the data. I. Vicente-Olabarria performed and interpreted the MRI studies.

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References

1. Le LT, Spudich SS. HIV-associated neurologic disorders and central nervous system opportunistic infections in HIV. *Semin Neurol* 2016;36:373–381.
2. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol* 2014;13:167–177.
3. Hara M, Martinez-Hernandez E, Arino H, et al. Clinical and pathogenic significance of IgG, IgA, and IgM antibodies against the NMDA receptor. *Neurology* 2018;90:e1386–e1394.
4. Ferretti F, Gisslen M, Cinque P, Price RW. Cerebrospinal fluid HIV escape from antiretroviral therapy. *Curr HIV/AIDS Rep* 2015;12:280–288.
5. Lamb CJ, Lopez Chiriboga AS, Sotello Aviles DA, Mendez JC, Robinson MT. Clinical Reasoning: a 46-year-old man with persistent hiccups, cognitive dysfunction, and imbalance. *Neurology* 2017;89:e193–e196.
6. Zarkali A, Gorgoraptis N, Miller R, et al. CD8+ encephalitis: a severe but treatable HIV-related acute encephalopathy. *Pract Neurol* 2017;17:42–46.
7. Dalmau J, Graus F. Antibody-mediated encephalitis. *N Engl J Med* 2018;378:840–851.
8. Fan CF, McInnis R, Linas B, Bica I, Cervantes-Arslanian AM. NMDAR-encephalitis Masquerading as recurrent HIV-encephalitis with CSF escape in an HIV+ patient (P2.306). *Neurology* 2017;88(16 Supplement): P2.306.

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