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Letter to the Editor

An anti-NMDA receptor encephalitis mimicking an HIV encephalitis

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ABSTRACT

The incidence of HIV associated neurocognitive disorders (HAND) were reduced with the use of antiretroviral therapy. In case of neuropsychiatric symptoms, after elimination of all infections, auto-immune encephalitis could be evocated as a differential diagnosis. We describe a case of anti-N-Methyl-D-Aspartate receptor encephalitis in an HIV-1 infected woman.

1. Introduction

Prevalence of HIV associated neurocognitive-disorders (HAND) is estimated around 20% in HIV-infected patients with suppressed HIV viraemia [1]. The most common causes are infectious encephalitis [2,3]. Since 2007, anti-N-Methyl-D-Aspartate receptor (anti-NMDAR) autoimmune encephalitis had been described as a major differential diagnosis of infectious encephalitis [4].

2. Case history

We present a 47-year-old Caucasian HIV-1 infected woman. She started antiretroviral therapy (ART) in 2008 simplified on July 2014 to a monotherapy of boosted darunavir (800 mg/day). Early 2015, she presented progressive psychiatric symptoms, including anorexia, insomnia, abnormal behavior, change of mood with a progressive loss of memory in a context of alcoholism. On May 2015, plasma HIV RNA was 62 copies/mL with 625/mm^3 (35%) of CD4 cells. In July 2015, a psychiatrist treated her with escitalopram for a depression.

In September 2015, she was admitted in emergency for behavioral disorders after three months of ART discontinuation. Neurologic examination revealed anxiety,agitation, temporo-spatial disorientation, anterograde amnesia, dysexecutive and discrete cerebellar syndrome, dysarthria and ageusia (Table 1). Lumbar puncture showed a meningitis with 48 cells (42% of neutrophils, 30% of lymphocytes, 28% of others cells), a slight increase of protids (0.6 g/L) and normal glycorrhachia. HIV RNA in cerebrospinal fluid (CSF) was 37,755 copies/ml versus 97,156 copies/ml in blood (Table 1). Electroencephalogram (EEG) showed a background of diffuse slow waves. Cerebral magnetic resonance imaging (MRI) revealed nonspecific increased signal on T2-weighted FLAIR imaging in the supratentorial white substance. HIV encephalitis was evocated after excluding other diagnoses, despite discordant viral load between CSF and plasma. We introduced foscarnet (180 mg/kg/day for 7 days) associated with emtricitabine/tenofovir and dolutegravir. Foscarnet was then switched to maraviroc (no tropism available, 300 mg bid).

The neuropsychiatric follow-up was described in Table 1. An episode of coma occurred induced by the introduction of benzodiazepines for her anxiety. The cerebral CT scan was normal. The EEG showed an overload pattern of theta-delta waves with moderate voltage, with a slight left predominance, without epileptic grapho-elements.

The lumbar puncture performed thereafter showed a significant decrease of HIV RNA (242 copies/mL), 15 elements (only lymphocytes), 0.56 g/L of protids and an IgG intrathecal synthesis with oligoclonal bands (Table 1). Because of this atypical presentation of HAND associated with a coma, we looked for autoimmune encephalitis and found out that anti-NMDAR antibodies were positive in CSF by indirect immunofluorescence with transfected cells (Euroimmun®, Germany), confirming the diagnosis of anti-NMDAR encephalitis. Body CT scan and pelvic MRI eliminated an ovarian teratoma or other neoplasia. The patient was treated by intravenous immunoglobulins (IVIG) during six months, associated to ART. After achieving undetectable HIV RNA in CSF, maraviroc was stopped and patient switched to a single tablet regimen with lamivudine/abacavir/dolutegravir. After 4 IVIG cures combined to neurological rehabilitation, we observed a full recovery of cognitive functions and behavior evaluated on MMSE (Mini-Mental State Evaluation), FAB (Frontal Assessment Battery) and clinical examination (Table 1). EEG was improved and showed only a slower asymmetric background activity on the right side. The brain MRI remained unchanged. Anti-NMDAR antibodies went back as negative in CSF (Table 1).

3. Discussion

We report the case of an anti-NMDAR encephalitis in an HIV-infected woman. Two cases with undetectable HIV RNA have been described in 2017 involving a 22-year-old man screened after a first episode of psychosis [4] and a 36-year-old woman with a severe encephalitis unresponsive to empirical anti-infectious therapy [5].

After elimination of infectious causes of encephalitis, we first suspected an HIV encephalitis. According to DSM V classification, this presentation could have been attributed to a complicated depression. Nevertheless, she was unresponsive to antidepressants and neurologic features led us to explore auto-immune causes [6]. Several criteria belonged to anti-NMDAR encephalitis [6]: female, abnormal behavior, speech dysfunction, central hypoventilation revealed by using benzodiazepines, CSF pleiocytosis, oligoclonal bands. Thediagnosis was confirmed by the positivity of anti-NMDAR antibodies in CSF with a qualitative test (no recognized threshold in the literature). We supposed that behind this obvious HIV encephalitis was hidden an anti-NMDAR encephalitis. Because we treated both of them at the same time, it was

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Table 1
Evolution of neuropsychological follow-up and immunovirological parameters in blood and CSF.

Dates	09/29/15	10/02/15	10/19/15	11/25/15 to 03/29/16	06/28/16
IVIG cures	0	0	1	2–6	ND
Neuro-psychological signs	Depression, anxiety, agitation, ageusia, dysarthria, dysexecutive syndrome, cerebellar syndrome, anterograde amnesia, TSD, insomnia	Depression, anxiety, agitation, dysarthria, ageusia, anterograde amnesia, TSD, insomnia	Anxiety, dysarthria, insomnia, memory impairment	Anxiety, insomnia, memory impairment	Normal
MMSE	21/30	19/30	24/30	27 to 29/30	30/30
FAB	9/18	13/18	14/18	15 to 18/18	ND
CD4/mm^3	433	ND	405	552	609
Viral load in plasma (copies/mL)	97,156	ND	192	20 to 63	55
Viral load in CSF (copies/mL)	37,755		242	20	ND
Elements in CSF (/mm^3) Proteins (g/L)	48 42% PNN 30% lymphocytes 28% others cells 0.6		15 0 PNN 100% lymphocytes 0.54		2 0.46
Anti-NMDAR antibody in CSF	ND	ND	Positive	ND	Negative

IVIG = intravenous immunoglobulins, ND = Not Done, TSD = temporo-spatial disorientation, MMSE = Mini-Mental State Evaluation, FAB = Frontal Assessment Battery, CSF = cerebro-spinal fluid, PNN = polynuclear neutrophils, NMDAR = *N*-methyl-D-Aspartate receptor.

difficult to exclude with certainty a concomitant HIV encephalitis.

HIV, as other neurotropic viruses (eg, HSV), might be a trigger for anti-NMDAR encephalitis [6] but the physiopathology of this link needs to be clarify. HIV-1 glycoprotein gp120 is a major virulence protein implicated in HAND. NMDA receptors, controlling synaptic plasticity and memory, are activated by phosphorylation of their NR1 subunit, which is decreased by gp120 [7]. The mechanism seems to be reversible in absence of gp120. We could therefore hypothesize that an elevated HIV RNA in CSF might participate to the dysfunction of NMDA receptors and explain cognitive symptoms. Nevertheless, given the chronology of events and the dynamics of plasma viral load (Table 1), HIV RNA in CSF had to be low at the beginning of the neuropsychiatric symptoms. The patient might have discontinued ART according to neurocognitive disorders linked to anti-NMDAR encephalitis.

The research of an underlying tumor, particularly ovarian teratoma in women or testicular germ-cell tumor in men, is of paramount importance in the context of an anti-NMDAR encephalitis. No tumor was found in our patient. The first line therapy relies on bolus of steroids, IVIG, or plasma exchanges, alone or combined during 5 days. This management seems to be efficient in 97% of cases if the tumor has been removed, 48% if not [8]. The second line therapy consists in using rituximab combined in the most severe cases with 6 months cycle of cyclophosphamide. We treated our patient by IVIG as proposed by Gastaldi et al. [9] and modified the ART, added foscarnet switched by maraviroc for their possible immunomodulatory properties and high concentrations in CSF according to a possible HIV encephalitis [10]. No relapse had occurred after a 2-years follow-up.

Anti-NMDAR encephalitis is now described as the most important cause of undetermined encephalitis and should be screened in HIV-infected patients with acute cognitive alteration, speech dysfunction, abnormal behavior and/or psychiatric symptoms.

Declarations of interest

None.

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