Opsoclonus-myoclonus-ataxia syndrome associated with central nervous system HIV-1 escape phenomenon

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Introduction. Opsoclonus-myoclonus-ataxia (OMA) syndrome is a rare neurological disorder characterized by involuntary conjugate saccadic eye movements, myoclonus, and ataxia. Few reports exist on patients with HIV and OMA.

Case report. A 41-year-old man diagnosed with HIV-1 infection in 1997 coursed with multiple anti-retroviral schemes as a consequence of poor adherence. In 2008 he presented an HIV-1 viral load of 100,000 copies/mL and a CD4+ T cell count of 10 cells/mm^3. In 2013 our patient arrived with an 11-month history of progressive opsoclonus and ataxia. He had undetectable plasma HIV-1 RNA load and CD4+ of 606 cells/mm^3. No opportunistic infections were found. Cerebrospinal fluid analysis showed mildly elevated protein concentration and HIV-1 viral load of 534 copies/mL. Cerebrospinal fluid co-receptor tropism test showed selective CCR5 usage. A brain magnetic resonance imaging showed hippocampal atrophy and T2-weighted hyperintensities. Our patient exhibited a dramatic recovery and cerebrospinal fluid HIV clearance after adjustment of anti-retroviral treatment based on genotyping resistance and tropism analyses.

Conclusions. In patients with HIV presenting cengral nervous system dysfunction without opportunistic infections, cerebrospinal fluid and plasma HIV-1 viral load, resistance and tropism tests should be performed to assess a potential viral escape and to design the appropriate anti-retroviral therapy in an individual patient basis.

Key words. Ataxia. Central nervous system. HIV. Myoclonus. Opsoclonus. Virus.

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Introduction

Opsoclonus-myoclonus-ataxia (OMA) syndrome is a distinctive neurological disorder characterized by involuntary, rapid, continuous, chaotic and multidirectional conjugate ocular movements without intersaccadic interval, that are present during fixation, smooth pursuit, and convergence, persisting during sleep or eyelid closure [1]. These movements usually cause oscillopsia and visual blurring. The syndrome also comprises generalized myoclonic jerks, as Kinsbourne originally described it in 1962 [2]. Opsoclonus is always central to the syndrome, which sometimes may present without myoclonus or ataxia, or even include postural tremor, encephalopathy, behavioural disturbances and a variety of neuropsychological impairments. This sets the basis for the more comprehensive term OMA. A variety of neuropsychological impairments can also be observed [1].

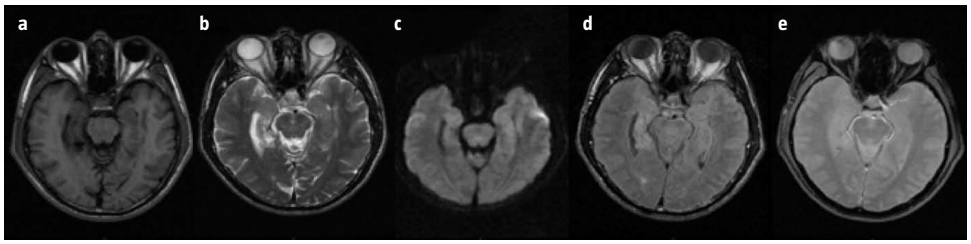
OMA in children is predominantly a paraneoplastic syndrome associated with neuroblastoma. Post-infectious OMA can also occur, mostly associated with viral aetiologies (e.g., herpes, mumps, influenza, dengue and West Nile viruses). In adults, OMA syndrome is rare and the causes are varied, including parainfectious and paraneoplastic encephalitis associated mainly with lung and breast cancers [3]. Apart from idiopathic, other miscellaneous causes can include multiple sclerosis, meningitis, intracranial tumours, hydrocephalus, thalamic haemorrhage, systemic diseases (AIDS, celiac disease, viral hepatitis, sarcoid), allogeneic hematopoietic stem cell transplantation, hyperosmolar coma and toxins [1,3,4]. The pathophysiology is uncertain, and the neuroanatomical correlate has been debated, but it most frequently implies lesions in the cerebellum, midbrain, thalamus or the paramedian pontine reticular formation [3].

Few reports exist on patients living with HIV/AIDS and OMA syndrome. They include the following clinical scenarios: at the time of seroconversion or acute HIV infection, as part of the immune reconstitution inflammatory syndrome, and at the time of a concurrent opportunistic CNS infection [5-7].

Case report

A 41-year-old man was diagnosed with HIV-1 infection in 1997. He received multiple anti-retroviral

Figure. Brain MRI images showing an enlarged temporal horn of the right lateral ventricle, corresponding with a reduced-volume hippocampus with high signal abnormalities on T_2-weighted sequences ('gliotic appearance'): a) Axial T_1-weighted image; b) Axial T_2-weighted image; c) Axial diffusion-weighted image; d) Axial T_2 FLAIR image; e) Axial T_2*-weighted image.



(ARV) combinations that included reverse transcriptase, protease and fusion inhibitors due to virological failure as a consequence of poor adherence. The patient was first referred to our institution in 2008 with an HIV-1 viral load of 100,000 copies/mL, and a CD4+ T cell count of 10 cells/mm^3. A diagnosis of HBV coinfection was also established. An ARV regime with tenofovir/emtricitabine + darunavir/ritonavir + raltegravir was given on the basis of plasma HIV-1 genotypic resistance test (Table). HIV-1 co-receptor tropism assay in plasma showed dual usage (i.e., both CCR5 and CXCR4 receptors). The patient had subsequent undetectable plasma viral loads and CD4+ T cell counts > 200 cells/mm^3.

The patient arrived to the Emergency Department on November 2013 complaining of an 11-month history of progressive dizziness, oscillopsia, and generalised tremor and walking difficulties. At presentation, neurological exam revealed an anxious patient with slurred speech and wide, erratic, multidirectional, spontaneous eye movements present with primary gaze and lacking intersaccadic interval. Additional neurological findings were truncal ataxia, wide-based gait and generalized tremor with a predominant postural component. The OMA syndrome was established. Laboratory exams revealed undetectable plasma HIV-1 RNA load (analytical sensitivity: 40 copies/mL) and CD4+ T cell count of 606 cells/mm^3, a negative VDRL test result, and positive results for both HBsAg and HBeAg antigens, with undetectable HBV DNA load. A contrast-enhanced brain CT scan was non-contributing. The CSF analysis revealed a mildly elevated protein concentration (57 mg/dL), with normal glucose (CSF/plasma glucose ratio of 0.53) and cell content (0 cells/mm^3). CSF smears revealed no organisms on Gram, India ink and Ziehl-Neelsen stains. Polymerase chain reaction assays for the presence of CMV, HSV, VZV and *Mycobacterium tuberculosis* in CSF did not amplify microbial genomes. Culture of CSF samples did not show microbe growth. Adenosine deaminase (ADA) activity on CSF was 0.1 U/L (non contributing test result). A brain MRI showed a reduced volume of the right hippocampus on T_1-weighted sequence with corresponding high signal abnormalities on T_2-weighted sequences (Figure). On contrast administration, no enhancing lesions were observed. A video-EEG did not detect any epileptic activity.

A whole body CT scan and colonoscopy were performed to search for the aetiology of OMA syndrome, showing no evidence of neoplasm. Intravenous steroids (three doses of 500 mg IV methylprednisolone) were administered without any clinical improvement. Determinations of anti-Hu, anti-Yo, and anti-Ri onconeural antibodies in CSF and plasma were also nonreactive. A second spinal tap showed a CSF protein concentration of 56.7 mg/dL. CSF HIV-1 viral load was 534 copies/mL. Comparative results of HIV genotypic resistance in plasma and CSF are shown in table. Co-receptor tropism test in CSF showed selective CCR5 usage. Based on the interpretation of the plasma and CSF molecular assays, ARV treatment was modified by adding etravirine and maraviroc to the previous regime. Considering the activity and CNS penetration of the ARV drugs this regime provided a score of 8 in the CNS Penetration-Effectiveness Rank (CPE; the sum of individual drug scorings based on known CNS penetrance patterns) [8], which according to previous evidence predicted a high probability of viral clearance in CSF. Consequently, we observed an impressive resolution of OMA syndrome over the first 6 months coinciding with clearance of HIV-1 viral load

Table. Plasma and CSF HIV-1 genotypic resistance in a 41-year-old man with HIV infection and opsoclonus-myoclonus-ataxia syndrome [a].

	Plasma			Cerebrospinal fluid		
	Drug resistance mutations	Level of drug resistance		Drug resistance mutations	Level of drug resistance	
		High-level resistance	Low-level resistance		High-level resistance	Low-level resistance
NRTI	M41L, L74V, M184V, L210W, T215Y	3TC, ABC, AZT, D4T, DDI, FTC, TDF	–	M41L, L74V, M184V, L210W, T215Y	3TC, ABC, AZT, D4T, DDI, FTC, TDF	–
NNRTI	K103S, G190A, F227L	EFV, NVP	ETR, RPV	K103S, G190A, F227L	EFV, NVP	ETR, RPV
PI	M46L, I54V, V82A, I84V	ATV/r, FPV/r, IDV/r, LPV/r, NFV, SQV/r, TPV/r	DRV/r	M46L, I54V, I84V	ATV/r, FPV/r, IDV/r, LPV/r, NFV, SQV/r, TPV/r	–
Integrase inhibitors	–	–	–	E157Q	–	EVG, RAL

[a] Plasma resistance tests were performed in 2008, before tenofovir/emtricitabine + darunavir/ritonavir + raltegravir regime was instituted. Cerebrospinal fluid resistance tests were performed in 2013, before the addition of etravirine and maraviroc to the previous regime. All virology assays were performed in the Laboratory of Molecular Virology of our center as follows: Viral load with RealTime HIV-1 Abbott Molecular Inc. ARV genotypic resistance test with ViroSeq TM HIV-1 Genotyping System v2.0 Celera corporation, with a modification in entry volume to 1.0 mL, and centrifugation parameters (initial time 2 h, 17000 rpm, 4 °C), volume adjusted to 25 μL for RNA suspension when viral load < 1000 copies/mL. Interpretation of the resistance pattern was performed with the Stanford HIV db Program Genotypic Resistance Interpretation Algorithm v7.0. HIV-1 co-receptor tropism assays were performed by using HIV-1 V3 loop amplicons with primers as described by the HIV French Resistance Group [9], with the interpretation algorithm Geno2Pheno v2.5. 3TC: lamivudine; ABC: abacavir; AZT: zidovudine; D4T: stavudine; DDI: didanosine; FTC: emtricitabine; TDF: tenofovir; EFV: efavirenz; NVP: nevirapine; ETR: etravirine; RPV: rilpivirine; ATV/r: atazanavir/ritonavir; FPV/r: fosamprenavir/ritonavir; IDV/r: indinavir/ritonavir; LPV/r: lopinavir/ritonavir; NFV: neflvinavir; SQV/r: saquinavir/ritonavir; TPV/r: tipranavir/ritonavir; DRV/r: darunavir/ritonavir.

on CSF. At 12-month follow-up the patient had no clinical evidence of OMA syndrome.

Discussion

To the best of our knowledge, we report the first case of OMA syndrome in a patient living with HIV, whose clinical manifestations were not related with an opportunistic infection, but rather a manifestation of CNS viral escape phenomenon. Our patient exhibited evidence of clinical recovery and HIV clearance in CSF after adjustment of ARV treatment based on CSF/plasma viral loads, genotypic resistance markers and tropism tests. Our findings suggest that measurement of CSF HIV-1 viral load and treatment with CNS-penetrating HAART should be instituted for patients with undetectable plasma HIV-1 viral load presenting with neurologic complaints in the absence of CNS opportunism, independently of CD4+ T cell count.

Just as other reservoirs of HIV, CNS can be a sanctuary for viral quasispecies with a different resistance pattern compared with viral species identified in plasma, especially in patients exposed to multiple ARV regimes [8]. Penetration of ARV drugs into the CNS is essential to achieve CSF HIV-1 RNA suppression. Suboptimal antiretroviral drug penetration in CNS may promote continuous viral replication, subsequent selection of drug-resistant mutants and neurological damage.

In the present case, the ARV regime was adjusted based on HIV-1 viral CSF/plasma loads, tropism and drug resistance tests and taking into account the CPE rank proposed by Letendre et al [8], which is based on physicochemical, pharmacokinetic and pharmacodynamic drug properties, and on drug effectiveness to attain HIV-1 suppression in CSF. In our patient the CPE score rose from 3 to 8 with the adjustment of the ARV regime, which crosses the recommended threshold value of 7. Despite the fact that CPE rank does not perfectly correlate with HIV-1 detectability in CSF [8], it represents a useful tool for the evaluation of penetrance and efficacy of antiviral drugs in CNS. Apart from inference on CNS drug penetrance pattern, we propose to perform HIV-1 tropism and genotypic resistance assays in both plasma and CSF in similar scenarios for individual design of the ARV regime.

The pathophysiology of HIV-associated OMA syndrome in the context of CSF HIV-1 escape phenomenon is uncertain. It can be hypothesized that OMA syndrome and other neurologic manifestations could be the consequence of dysregulated inflammation consisting in a reduced CD4+/CD8+ T cell ratio in association with a preserved critical level

of functional CD4+ T cells for efficient CD8+ cytotoxicity, which results in dysfunction of brainstem-cerebellar circuitry in susceptible individuals [8]. The emergence of a discordant HIV suppression between plasma and CSF causing neurologic manifestations is only beginning to be recognized. In 2003 Wendel and McArthur reported three cases of acute meningoencephalitis in patients with chronic HIV infection [9]. The three patients had elevated HIV-1 CSF/plasma ratio and T_2-weighted signal abnormalities on brain MRI, exhibiting a dramatic responses to ARV therapy. Canestri et al [10] have also described the CSF viral escape phenomenon in 11 patients with neurologic symptoms. CSF viral escape is a rare phenomenon characterized by the discordance between plasma and CSF HIV-1 RNA levels with any detectable CSF HIV-1 RNA level > 200 copies/mL with plasma viral load < 50 copies/mL, or by a CSF HIV-1 RNA level ≥ 1 log greater than the plasma level in the setting of ARV treatment [10]. The modification of ARV therapy in these patients should achieve better virological effect on CSF with potential clinical improvement as a result of subsequent control of viral replication within CNS.

Recently, Vale et al [7] reported on a female diagnosed with AIDS 8 years before, who was on her second ARV regime presenting with OMA syndrome with a CD4+ T cell count of 537 cells/mm^3 and a non-detectable plasma viral load. She was treated symptomatically with clonazepam presenting mild improvement of vomiting, headache, ataxia, and opsoclonus, but with persistence of distal myoclonus in the upper limbs. Although it can be inferred that the case was similar to our patient, no HIV-1 viral load in CSF was determined [7]. Our patient showed no improvement with steroids, but there was a complete clinical response and clearance of HIV-1 viral load in CSF after modification of ARV regime based on tropism and resistance analysis.

In conclusion, this is the first report on OMA syndrome in a patient with AIDS as a probable manifestation of CSF HIV-1 escape phenomenon. The pathophysiology of HIV-associated OMA syndrome in this specific context remains uncertain. We propose that CSF viral escape phenomenon should be considered in HIV-infected patients without opportunistic infections and undetectable plasma HIV-1 viral load who present with clinical manifestations of CNS dysfunction. Consequently, ARV treatment should be adjusted according to genotypic resistance and tropism tests in CSF and plasma, as well as CPE rank scoring. Further investigations are needed to clarify the mechanisms mediating the CNS manifestations in patients with CSF viral escape phenomenon.

References

1. Wong A. An update on opsoclonus. Curr Opin Neurol 2007; 20: 25-31.
2. Kinsbourne M. Myoclonic encephalopathy of infants. J Neurol Neurosurg Psychiatry 1962; 25: 271.
3. Klaas JP, Ahlskog JE, Pittock SJ, Matsumoto JY, Aksamit AJ, Bartleson JD, et al. Adult-onset opsoclonus-myoclonus syndrome. Arch Neurol 2012; 69: 1598-607.
4. Anderson NE, Budde-Steffen C, Rosenblum MK, Graus F, Ford D, Synek BJ, et al. Opsoclonus, myoclonus, ataxia, and encephalopathy in adults with cancer: a distinct paraneoplastic syndrome. Medicine (Baltimore) 1988; 67: 100-9.
5. Van Toorn R, Rabie H, Warwick JM. Opsoclonus-myoclonus in an HIV-infected child on antiretroviral therapy –possible immune reconstitution inflammatory syndrome. Eur J Paediatr Neurol 2005; 9: 423-6.
6. Ayarza A, Parisi V, Altclas J, Visconti D, Persi G, Rugilo CA, et al. Opsoclonus-myoclonus-ataxia syndrome and HIV seroconversion. J Neurol 2009; 256: 1024-5.
7. Vale TC, Silva RA, Cunningham MC, Maia DP, Camargos ST, Cardoso F. Opsoclonus-myoclonus-ataxia syndrome in an AIDS patient. Einstein (Sao Paulo) 2013; 11: 533-4.
8. Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, et al. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol 2008; 65: 65-70.
9. Wendel KA, McArthur JC. Acute meningoencephalitis in chronic human immunodeficiency virus (HIV) infection: putative central nervous system escape of HIV replication. Clin Infect Dis 2003; 37: 1107-11.
10. Canestri A, Lescure FX, Jaureguiberry S, Moulignier A, Amiel C, Marcelin AG, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. Clin Infect Dis 2010; 50: 773-8.

Síndrome opsoclono-mioclono-ataxia asociado a fenómeno de escape viral por virus de la inmunodeficiencia humana en el sistema nervioso central

Introducción. El síndrome opsoclono-mioclono-ataxia (OMA) es un trastorno neurológico infrecuente caracterizado por movimientos oculares conjugados sacádicos involuntarios, mioclonías y ataxia. Existen pocos casos en la bibliografía de pacientes con virus de la inmunodeficiencia humana (VIH) y OMA.

Caso clínico. Varón de 41 años y diagnóstico de infección por el VIH-1 desde 1997, que cursó con múltiples esquemas antirretrovirales debido a una pobre adhesión al tratamiento. En 2008 presentó una carga viral de 100.000 copias/mL y una cuenta linfocitaria CD4+ de 10 células/mm^3. En 2013 sufrió un cuadro progresivo de 11 meses de evolución caracterizado por opsoclonía y ataxia. En ese momento, su carga viral era indetectable, y la cuenta de CD4+, de 606 células/mm^3. Se

descartaron infecciones oportunistas. El examen del líquido cefalorraquídeo demostró hiperproteinorraquia leve y una carga viral de 534 copias/mL. El examen del tropismo de correceptor en el líquido cefalorraquídeo demostró un uso selectivo de CCR5. La resonancia magnética cerebral objetivó atrofia hipocámpica e hiperintensidades en las secuencias ponderadas en T_2. El paciente mostró una recuperación clínica franca y un aclaramiento de la carga viral en el líquido cefalorraquídeo tras el ajuste de antirretrovirales basado en la resistencia de genotipo y el análisis de tropismo.

Conclusiones. En pacientes con infección por el VIH y disfunción del sistema nervioso central sin infecciones oportunistas, debería llevarse a cabo una determinación de la carga viral en el plasma y el líquido cefalorraquídeo para descartar un potencial fenómeno de escape viral, así como exámenes de resistencia y tropismo para diseñar el tratamiento antirretroviral adecuado.

Palabras clave. Ataxia. Mioclono. Opsoclono. Sistema nervioso central. VIH. Virus.