

Sustained Disease-Activity-Free Status in a Woman with Relapsing-Remitting Multiple Sclerosis Treated with Antiretroviral Therapy for Human Immunodeficiency Virus Type 1 Infection

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Abstract

A negative association between human immunodeficiency virus (HIV) Infection and multiple sclerosis (MS) is expected, as MS pathogenesis is triggered by auto-reactive T-cells, which are depressed in case of HIV Infection. Furthermore, there is increasing evidence that HIV-Infected MS patients may benefit from antiretroviral therapy.

We report the case of a woman suffering from relapsing-remitting MS (RR-MS) who contracted HIV-1 Infection while she was treated with low-dose interferon (IFN) beta-1a since five years. With combination antiretroviral therapy (cART) in addition to IFN beta-1a, the patient had normal CD4+ cell counts, undetectable viral load, and no more clinical and radiological evidence of MS activity.

The reason why HIV Infection has a protective role for developing MS, and how antiretroviral therapy is effective in modifying MS course are intriguing questions which need further investigations.

Keywords: Antiretroviral; HIV; HERV; Interferon-beta; Multiple sclerosis

Introduction

A recent comparative cohort study conducted in the UK has reported a negative association between human immunodeficiency virus (HIV) Infection and multiple sclerosis (MS) [1]. This finding is expected since MS pathogenesis is triggered by auto-reactive T-cells, which are suppressed by HIV Infection. Furthermore, there is increasing evidence that HIV-Infected MS patients may benefit from antiretroviral therapy.

The case of a woman suffering from relapsing-remitting MS (RR-MS) who secondarily became HIV-1 seropositive, while already treated with high-dose interferon (IFN)-beta-1a for five years, is reported. With combination antiretroviral therapy (cART) in addition to low-dose IFN-beta-1a, the patient had normal CD4+ cell counts, undetectable viral load, and no more clinical and radiological evidence of MS activity. The possible mechanisms that may contribute to this outcome are discussed.

Case Report

A 19-year-old African woman living in Switzerland, with no past medical history, developed a left optic neuritis in September 2006. The diagnostic workup was significant for the presence of immunoglobulin G (IgG) oligoclonal bands in the cerebrospinal fluid (CSF), without corresponding IgG in the serum. HIV serology was negative.

Brain magnetic resonance imaging (MRI) showed several supratentorial and infratentorial hyperintense white matter lesions (WML), distributed around the corpus callosum, periventricularly and subcortically on T2-weighted and fluid-attenuated inversion recovery images. Contrast enhancement was observed in one frontal lesion on T1-weighted sequence (Figure 1). The patient was treated with a 3-day course of intravenous methylprednisolone, with complete recovery.

In February 2007, the patient experienced left visual loss and reported daily pollakiuria. Neurological examination showed left optic disc pallor, jerky ocular pursuit movements, increased deep tendon reflexes in the left upper limb, tactile hypoesthesia and hypalgesia up to Th7 level. The Expanded Disability Status Score (EDSS) was 2.5. Visually evoked potentials showed a delayed P100 latency on the left side. A new

brain MRI showed multiple contrast-enhancing supratentorial and infratentorial WML, and spinal MRI showed one non-enhancing left spinal cord lesion at Th8 level (Figure 2). On the basis of this relapse and of MRI findings, MS diagnosis was confirmed according to the 2005 revised McDonald criteria [2].

In June 2007, the patient started high-dose IFN beta-1a (44 mcg 3 times weekly). In August 2008, HIV serology was checked because of contact with a HIV-Infected partner, and showed HIV negativity.

In October 2009, the patient had a new relapse characterized by sensory deficits of the left side of her body (EDSS = 2.0), which persisted until March 2012 (EDSS=1.5; no new MRI lesion). In May 2012, IFN beta-1a was discontinued because of persistent local side effects. As a treatment alternative, fingolimod (0.5 mg/day) was therefore proposed.

Baseline blood tests before initiation of fingolimod showed HIV-1 seroconversion. CD4+ cell count was 178/mm³. The patient was then started on low-dose IFN beta-1a treatment (30 mcg once a week) and combined antiretroviral therapy (cART), including tenofovir, emtricitabin, and etravirine.

In June 2012, the patient suffered from oral candidiasis. CD4+ cell count was 265/mm³. In April 2013 the nadir of CD4+ count (136/mm³, 31% of total lymphocytes) was reached, but viremia was undetectable. Subsequently, CD4+ cell counts began to progressively increase up to 505/mm³ (37% of total lymphocytes) in June 2015. Viremia was stably undetectable, with no evidence of opportunistic Infections.

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Received July 30, 2015; **Accepted** September 03, 2015; **Published** September 10, 2015

Citation: Maulucci F, Schlupe M, Granziera C (2015) Sustained Disease-Activity-Free Status in a Woman with Relapsing-Remitting Multiple Sclerosis Treated with Antiretroviral Therapy for Human Immunodeficiency Virus Type 1 Infection. J Mult Scler (Foster City) 2:152. doi:10.4172/2376-0389.1000152

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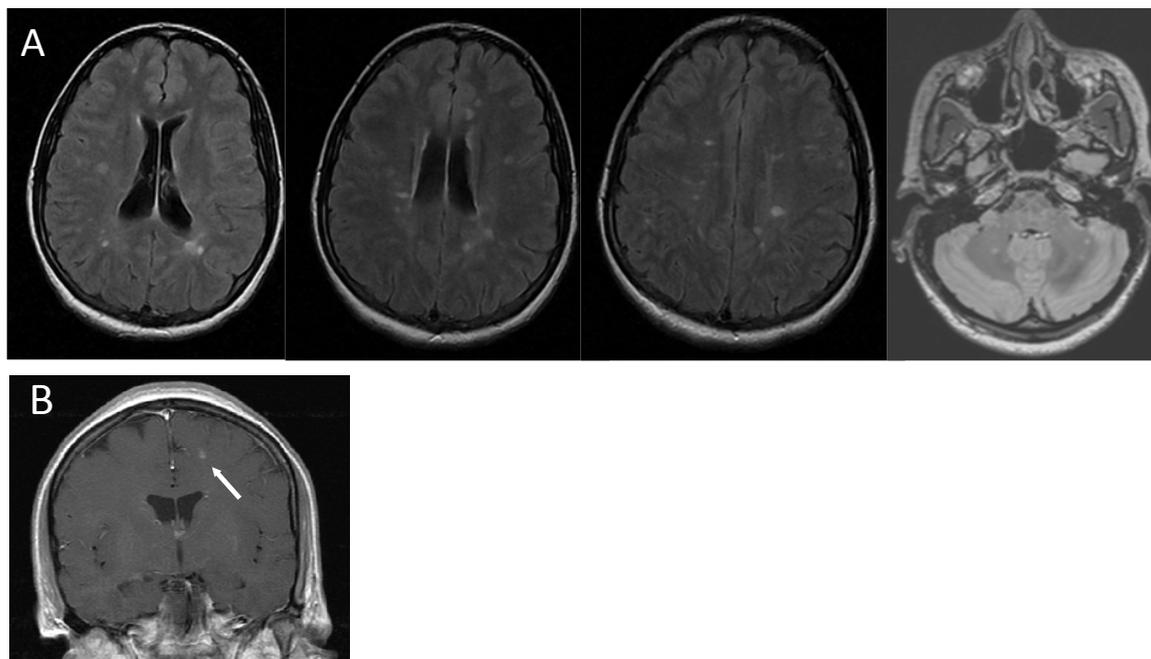


Figure 1: Brain MRI at baseline (September 2006).

A: Axial FLAIR demonstrated diffuse supratentorial and infratentorial hyperintense white matter lesions, distributed around the corpus callosum (not showed here), periventricularly and subcortically.

B: Coronal T1 post-gadolinium showing contrast enhancement of a frontal lesion (arrow).

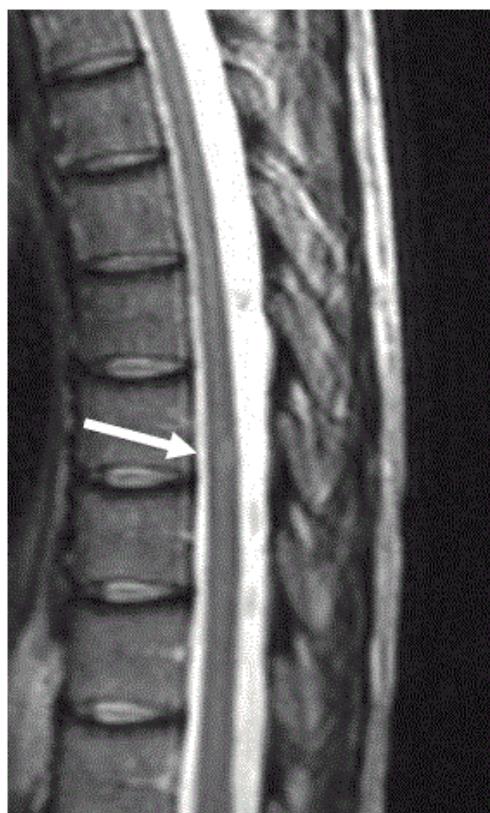


Figure 2: Spinal MRI at baseline (February 2007). Sagittal T2-weighted showing one non-enhancing left spinal cord lesion at D8 level (arrow).

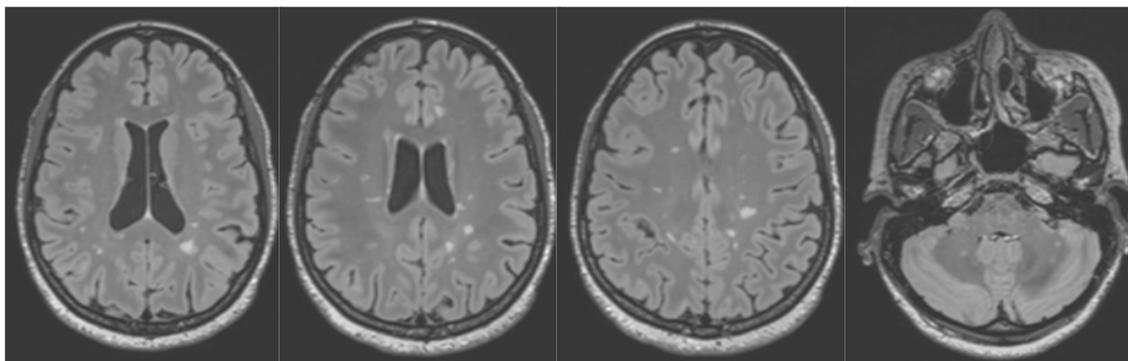


Figure 3: MRI of the brain at 8 year follow-up (June 2014). Axial FLAIR showed no evidence of radiological disease progression.

In parallel, MS remained stable, with a persistent minimal EDSS score of 1.5. No new relapse was recorded, and recent brain and spinal MRI showed stability of lesions without evidence of disease progression (Figure 3).

Discussion

To our knowledge, this is the first report of a patient developing HIV-1 seropositivity while already receiving IFN beta treatment for RR-MS.

Since the first presentation, the patient showed clinical and MRI disease activity and still experienced one sensory relapse in 2009, prior to HIV Infection and while receiving high-dose IFN beta-1a. No more relapse was recorded following this. Most importantly, neither relapse nor clinical nor radiological progression was observed after seroconversion in 2012, and after the patient was started on low-dose IFN beta-1a combined with cART.

Interestingly, although low-dose IFN beta is known to be less effective than high-dose IFN beta on recurrence of relapses and on radiological disease progression [3], since 2012 the patient has achieved “no evidence of disease activity” (NEDA), defined as the absence of new or enlarging T2 lesions or T1 gadolinium-enhancing lesions on MRI and no sustained EDSS score progression or clinical relapse [4].

It can be hypothesized that both HIV Infection and cART may have contributed to this favorable outcome, as suggested by recent studies.

The links between retroviral Infection, antiretroviral treatment, MS autoimmunity and IFN beta-1a treatment are not clear.

It has long been postulated that viral Infections may have a role in initiating central nervous system (CNS) demyelinating disorders, including MS. Furthermore, it has been hypothesized that acquired retroviral Infections may contribute to the development of MS or trigger it [5] as endogenous retroviruses (HERVs) may do [6–10].

On the other hand, immunodeficiency induced by the untreated HIV Infection may contribute to prevent development of MS or reduce MS activity. A recent comparative cohort study conducted in the UK has reported a statistically significant negative association between HIV Infection and MS [1].

Furthermore, MS activity may be reduced by cART, through the suppression of HERV activity and/or even herpes virus replication [11]. It has been observed that MS is uncommon among HIV-positive cART-treated patients [12,13]. Few cases have been reported in which

HIV seropositivity was established at the same time as MS diagnosis [12,14–20]. Two out of the three patients who benefitted of cART (none of them benefitted of a MS-specific therapy) showed lack of MS progression once they were started on cART [12,20]. There is an ongoing clinical trial attempting to establish whether raltegravir, an integrase inhibitor that blocks retroviral replication, may ameliorate the course of RR-MS [21].

Even other CNS demyelinating disorders may improve with cART, as reported in a HIV-1 Infected patient with overlapping features of MS and neuromyelitis optica [22].

Our patient was treated with tenofovir, as the patient of Chalkley et al. [20] was. Tenofovir may show a supplementary effect on MS activity compared to others antiretroviral drugs, since it is administered in the form of a prodrug containing fumarate, which is the active ingredient of dimethyl fumarate recently approved for the treatment of RR-MS.

Unlike the cases previously reported in the literature, our patient was already treated with IFN beta-1a before the HIV Infection. This drug is not only a disease-modifying therapy approved for the treatment of MS, but seems to be capable of controlling HIV-1 replication [23] and preventing simian immunodeficiency virus Infection [24]. Furthermore, IFN may decrease MS activity through the decrease of the serum reactivity to multiple HERVs [25] as antiretroviral drugs may do.

In summary, IFN beta-1a and HIV-Infection treated with cART may have contributed to stabilize MS course in our patient, leading to an enduring benefit at 9-years follow-up. Future studies should attempt at establishing the long-term benefits and risks of such a combined therapy, and at investigating the complex interplay between retroviral Infection, cART and MS.

Acknowledgements

The authors are grateful to Professor Renaud Du Pasquier for his critical reading of the manuscript.

References

1. Gold J, Goldacre R, Maruszak H, Giovannoni G, Yeates D, et al. (2015) HIV and lower risk of multiple sclerosis: Beginning to unravel a mystery using a record-linked database study. *J Neurol Neurosurg Psychiatry* 86: 9-12.
2. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, et al. (2005) Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria”. *Ann Neurol* 58: 840-846.
3. Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, et al. (2002) Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. *Neurology*.

4. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL (2015) Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. *JAMA Neurol* 72: 152-158.
5. Koprowski H, DeFreitas EC, Harper ME, Sandberg-Wollheim M (1985) Multiple sclerosis and human T-cell lymphotropic retroviruses. *Nature* 318: 154-160.
6. Perron H, Jouvin-Marche E, Michel M, Ounanian-Paraz A, Camelo S, et al. (2001) Multiple sclerosis retrovirus particles and recombinant envelope trigger an abnormal immune response in vitro, by inducing polyclonal Vbeta16 T-lymphocyte activation. *Virology* 287: 321-332.
7. Nexo BA, Christensen T, Frederiksen J, Moller-Larsen A, Oturai AB, et al. (2011) The etiology of multiple sclerosis: genetic evidence for the involvement of the human endogenous retrovirus HERV-Fc1. *PLoS One* 6: e16652.
8. Nissen KK, Laska MJ, Hansen B, Terkelsen T, Villesen P, et al. (2013) Endogenous retroviruses and multiple sclerosis-new pieces to the puzzle. *BMC Neurol* 13: 111.
9. Derfuss T, Curtin F, Guebelin C, Bridel C, Rasenack M, et al. (2015) A phase IIa randomized clinical study testing GNBAC1, a humanized monoclonal antibody against the envelope protein of multiple sclerosis associated endogenous retrovirus in multiple sclerosis patients-A twelve month follow-up. *J Neuroimmunol* 285: 68-70.
10. Derfuss T, Curtin F, Guebelin C, Bridel C, Rasenack M, et al. (2015) A phase IIa randomized clinical study of GNBAC1, a humanized monoclonal antibody against the envelope protein of multiple sclerosis-associated endogenous retrovirus in multiple sclerosis patients. *Mult Scler* 21: 885-893.
11. Dreyfus DH (2011) Autoimmune disease: A role for new anti-viral therapies? *Autoimmun Rev* 11: 88-97.
12. Maruszak H, Brew BJ, Giovannoni G, Gold J (2011) Could antiretroviral drugs be effective in multiple sclerosis? A case report. *Eur J Neurol* 18: e110-111.
13. Nexo BA, Pedersen L, Sorensen HT, Koch-Henriksen N (2013) Treatment of HIV and risk of multiple sclerosis. *Epidemiology* 24: 331-332.
14. Berger JR, Sheremata WA, Resnick L, Atherton S, Fletcher MA, et al. (1989) Multiple sclerosis-like illness occurring with human immunodeficiency virus infection. *Neurology* 39: 324-329.
15. Garcia-Delange T, Sanchez-Gonzalez J, Romero-Crespo F, Colmenero JD (1995) Picture similar to multiple sclerosis and HIV Infection. *Enferm IFNecc Microbiol Clin* 13: 380-382.
16. Graber P, Rosenmund A, Probst A, Zimmerli W (2000) Multiple sclerosis-like illness in early HIV Infection. *AIDS* 14: 2411-2413.
17. Facchini SA, Harding SA, Waldron RL (2002) Human immunodeficiency virus-1 Infection and multiple sclerosis-like illness in a child. *Pediatr Neurol* 26: 231-235.
18. Duran E, Galvez J, Patrignani G, Izquierdo G (2004) Multiple sclerosis-like illness in a HIV-1 patient. *J Neurol* 251: 1142-1144.
19. Gonzalez-Duarte A, Ramirez C, Pinales R, Sierra-Madero J (2011) Multiple sclerosis typical clinical and MRI findings in a patient with HIV Infection. *J Neurovirol* 17: 504-508.
20. Chalkley J, Berger JR (2014) Multiple sclerosis remission following antiretroviral therapy in an HIV-Infected man. *J Neurovirol* 20: 640-643.
21. Giovannoni G (2013) Raltegravir (Isentress) Pilot Study in Relapsing Multiple Sclerosis
22. Delgado SR, Maldonado J, Rammohan KW (2014) CNS demyelinating disorder with mixed features of neuromyelitis optica and multiple sclerosis in HIV-1 Infection. Case report and literature review. *J Neurovirol* 20: 531-537.
23. Doyle T, Goujon C, Malim MH (2015) HIV-1 and interferons: Who's interfering with whom? *Nat Rev Microbiol* 13: 403-413.
24. Sandler NG, Bosinger SE, Estes JD, Zhu RT, Tharp GK, et al. (2014) Type I interferon responses in rhesus macaques prevent SIV Infection and slow disease progression. *Nature* 511: 601-605.
25. Petersen T, Moller-Larsen A, Thiel S, Brudek T, Hansen TK, et al. (2009) Effects of interferon-beta therapy on innate and adaptive immune responses to the human endogenous retroviruses HERV-H and HERV-W, cytokine production, and the lectin complement activation pathway in multiple sclerosis. *J Neuroimmunol* 215: 108-116.