Multiple Sclerosis and Subsequent Human Immunodeficiency Virus Infection: A Case with the Rare Comorbidity, Focus on Novel Treatment Issues and Review of the Literature

CHARALAMPOS SKARLIS¹, MARIA GONTIKA¹, SERAFEIM KATSAVOS¹, GIORGIOS VELONAKIS², PANAGIOTIS TOULAS² and MARIA ANAGNOSTOULI¹,³

¹Immunogenetics Laboratory, 1st Department of Neurology, Medical School of National and Kapodistrian University of Athens, Aeginition Hospital, Athens, Greece; ²Research Unit of Radiology and Medical Imaging, 2nd Department of Radiology, Medical School of National and Kapodistrian University of Athens, Eugenidion Hospital, Athens, Greece; ³Outpatient Section of Demyelinating Diseases Clinic, 1st Department of Neurology, Medical School of National and Kapodistrian University of Athens, Aeginition Hospital, Athens, Greece

Abstract. Background: The comorbidity between Multiple Sclerosis (MS) and Human Immunodeficiency Virus (HIV) infection is particularly rare. Only a few cases of comorbidity of Clinically Definite (CD)-MS and HIV have been documented worldwide, while the potential beneficial role of antiretroviral therapy regarding MS activity has long been an area of debate. Case Report: We present a 36-year old male, bearing a diagnosis of CD-MS for twelve years. He had been treated for ten years with interferon-beta-1b, when he voluntarily discontinued therapy, claiming clinical stability. One year later he was diagnosed positive for HIV and he started and continued only on efavirenz/emricitabine/tenofovir disoproxil fumarate (ATRIPLA®), remaining relapse-free until today. Conclusion: This fact, in combination with the unique pharmaceutical composition of the drug, which contains a component similar to a newly-approved agent for MS, dimethyl fumarate, prompted us to review the literature regarding this rare comorbidity and to suggest that the role of the antiretroviral therapy should be further explored in MS.

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Correspondence to: Ass. Prof. Maria C. Anagnostouli, Demyelinating Diseases Clinic & Director of Immunogenetics Laboratory, 1st Department of Neurology, Medical School, National and Kapodistrian University of Athens, Aeginition Hospital, 72-74 Vassilisis Sofias Ave, 11528, Athens, Greece. Tel: +30 2107289278, Fax: +30 2107216474, e-mail: managnost@med.uoa.gr

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time. Four months later, he was hospitalized at the same PH, because of an episode of acute right optic neuritis. His rest neurological examination is referred as normal. He was treated with 1 gr intravenous (IV) methylprednisolone for five days, followed by per os tapering, until total remission. At that time, the performed brain magnetic resonance imaging (MRI) revealed multifocal white matter T2 lesions, without gadolinium enhancement in T1 sequences, fulfilling the McDonald and Barkhof criteria, for Multiple Sclerosis (MS) (7). He refused lumbar puncture; therefore, the oligoclonal band status is still unknown.

The patient visited for the first time the Outpatient Department of our Clinic (OTC) a few months later, in 2004. His personal history was significant for chicken pox at the age of 16 years and childhood asthma. His family history was positive for autoimmune diseases, as his mother bore a diagnosis of Hashimoto’s disease. His neurological examination revealed only indifferent bilateral plantar reflexes. He had a full laboratory screening with no pathological results except for high levels of IgG immunoglobulin. He repeated brain MRI, which showed a new gadolinium enhanced parietal lesion, thus he initiated treatment with interferon beta-1b three times weekly, with satisfying responsiveness and tolerance.

During the following decade, he experienced two further clinical attacks, with an interval of two years. The first episode, in 2007, consisted of numbness of the upper extremities, with a hypoesthesia level at cervical level 5 (C5), fully remitted after three days of 1 gr IV methylprednisolone followed by per os tapering, at the PH. The second one, in 2009, consisted of left horizontal diplopia, partially improved after per os methylprednisolone treatment. During the second episode, his neurological examination revealed left horizontal diplopia and indifferent bilateral plantar reflex and his Expanded Disability Status Scale (EDSS) score was estimated at 2.00. The new MRI scanning showed non-active multifocal white matter lesions in both the brain and cervical spine, with one new periventricular lesion. In 2012, he voluntarily discontinued therapy, claiming of no symptoms and clinical stability. Until then, his Annualised Relapse Rate (ARR) was 0.44, his EDSS progression 0.22 and he had received three courses of cortisone, either intravenously or per os.

In 2014, he was hospitalized in the PH for a mild brain injury, after a conflict episode on the road. During his hospital evaluation, his initial blood tests showed white blood cell (WBC) 6.85 K/μl, lymphocytes (1.69 K/μl) and low platelets (60 K/μl) and subsequently, he was found positive for HIV. He initiated antiretroviral treatment with efavirenz (600 mg)/emricitabine (300 mg)/tenofovir-disoproxil fumarate (200 mg) (ATRIPLA®), one tablet once a day, with satisfying responsiveness. Regarding his MS course, he remained both clinically and neuro-radiologically stable. After eight months on ATRIPLA®, his WBC were 7.5 K/μl and his lymphocyte number was 1.90 K/μl and platelets 153 K/μl. His neuro-radiological scans were absolutely the same, as well (Figure 1). Today, after almost three years on this antiretroviral therapy, his ARR is 0.28, his EDSS progression 0.14, he demonstrates unidentifiable HIV blood-load, and he is fully functional, concerning activities of daily living (Table I).

**Literature Review**

The coexistence of demyelinating neurological disorders and HIV is particularly rare, especially regarding MS. In 1989,
Berger and collaborators were the first to describe a series of seven patients with an MS-like disease and HIV comorbidity (8, 9). Taking into consideration the primitive criteria of MS in 1989, we cannot be sure that these patients were suffering from MS per se, or another demyelinating disease. However, six definitive MS-HIV comorbidity cases, according to original and revised McDonald criteria, are presented in the international literature (10-15). In two reports, HIV infection was diagnosed after MS, while in those described from Chin and Facchini, HIV infection clearly preceded MS and only one the diagnosis was concomitantly (10-15). Regarding the gender of the patients, six males (including our case) and only one female are reported (Table II), in contrast to the typical finding of female prevalence in MS.

Interestingly, Maruszak et al. (2011) and Chalkley et al. (2014) describe improvement of neurological symptoms and no relapses in patients with MS and HIV infection, after receiving antiretroviral therapy (11, 12). The most striking element is that these patients showed no complications and disease progression for a long time, remaining clinically stable, similarly to the clinical status of our patient for the last two years. In 2015 Gold et al., in the largest linkage study undertaken to investigate a possible association between HIV and MS, revealed that HIV infection is associated with significantly decreased risk of developing MS (16).

**Discussion**

Our patient is the first clinical case in the literature, whose MS diagnosis significantly proceeds HIV infection with such a big interval. Although his total clinical course cannot be officially considered as a benign type of MS, his disease course is significant for very few relapses and minimal accumulative disability. The accidental result of HIV seropositivity, as well as the persistent stable clinical presentation while on monotherapy with highly active antiretroviral therapy (HAART), led as to investigate whether his clinical stability is associated with either the HIV infection per se, or with the possible effects of the HAART in MS. It is well known that concurrence of MS and HIV infection is uncommon and only six cases (fulfilling the McDonald criteria) have been reported, as presented in Table II.

Our case is the first of an MS patient with a following HIV infection treated with the novel antiretroviral drug ATRIPLA®. While on ATRIPLA® treatment, he remains relapse free, neurologically stable, and with undetectable viral load.

| Table I. Milestones of patient's clinical course and therapy. |
|---------------------------------------------------------------|
| Relapses | 2003 | 2004 | 2006 | 2007 | 2009 | 2014 | 2015 |
|-----------|------|------|------|------|------|------|------|
| 1. Numbness of lower extremities and trunk | Clinically stable | Clinically stable | | Clinically stable | | Clinically stable | |
| 2. Right optic neuritis | | | | | | | |
| EDSS | | | | | | | |
| Corticosteroids | | | | | | | |
| Referred as zero 5 g Methyl-prednisolone, per os tapering | | | 1.0 | 1.0 | | 3 g Methyl-prednisolone, per os tapering | |
| Brain MRI | | | | | | | |
| Multiple subcortical and periventricular lesions of both cerebral hemispheres | One new active left parietal lesion Gadolinium (+) | | | One new lesion of the cerebral hemispheres, one new lesion of the corpus callosum | | | T2 sequences stable |
| Cervical MRI | | | | | | | |
| | | | Three-Four intra-medullary lesions, mainly at C2-C3 and C4 levels. Gadolinium (–) | | | Stable | Stable |
| Thoracic MRI | | | | | | | |
| | | | | | | | |
| DMT | | | | | | | |
| Interferon-b-beta | | Interferon-b-beta | | | | | |
| HAART | | | | | | | |
| | | | | | | | |
| DMT, Disease modifying therapy; HAART, high active antiretroviral therapy; EDSS, expanded disability status scale; MRI, magnetic resonance imaging; Gd, gadolinium.
It is known, that the mechanism of action of efavirenz is through non-competitive inhibition of the HIV reverse transcriptase (17). Moreover, the mechanism of action of both tenofovir-disoproxil-fumarate (nucleotide reverse transcriptase inhibitor) and emtricitabine (nucleoside reverse transcriptase inhibitor) is based on the intracellular conversion of these drugs to their active metabolites, which competitively inhibit the activity of HIV reverse transcriptase and consequently block viral replication (17,18). In this way, the drug restores the number of CD4+ lymphocytes interfering with immune-modulation. Regarding our patient, we cannot ignore the fact that fumarate is a component of ATRIPLA® as tenofovir-disoproxil-fumarate. Chalkley and colleagues also report the same clinical effect in their clinical MS-HIV case treated with fumarate, which contains the fumarate (11).

Fumarate was recently approved by FDA as dimethyl-fumarate for MS treatment. It exerts its immunomodulatory effect by reducing the expression of cytokines tumor necrosis factor-a (TNF-a), interleukin- 1β (IL-1β), and interleukin-6 (IL-6) in glial cells, and also by mediating a strong antioxidant effect (19-23). Although it is not available in the international literature and we cannot confirm in any way the bioequivalence of these two components, the disoproxil-fumarate might somehow act as an immunomodulatory agent, leading to clinical stability. However, this working hypothesis requires extensive research.

An MS-like illness has been previously described in association with HIV-1 infection with a clinical syndrome indistinguishable from MS (9,10). Taking into consideration the primitive criteria of MS in 1989, we cannot be sure that these patients were suffering from MS per se or another demyelinating disease. Reviewing the reports which fulfill the McDonald criteria we can notice that six patients were males (including our case) and only one was female, in contrast to the typical finding of female prevalence in MS. The clinical course of the patients presented was relapsing-remitting MS, in the majority of the cases (3 cases including ours). Except for one, adult patients received antiretroviral therapy and claimed clinical stability. Interestingly, Maruszak and Chalkley described improvement of MS symptoms and no relapses in their patients after initiation on antiretroviral therapy remaining clinically stable for 12 and 8 years respectively, receiving only HAART (11, 12).

Several explanations of the patient’s clinical course can be supposed. First, immunodeficiency induced by HIV itself (even in the absence of antiretroviral treatment) may prevent the deterioration of MS. In specific, HIV harms immune-cell homoeostasis and targets a wide range of immune cells (CD4+, CD8+) and signaling pathways overlapping with MS pathogenesis (24-31). HIV infection selectively depletes CD4+ T cells, and therefore it may be considered protective against the occurrence of MS.

Second, as it is widely accepted, a decrease in regulatory T cells (Treg) drives CNS injury in MS, which is in part mediated by autoreactive CD4+ T lymphocytes, in addition to increased T-helper 17 cells (Th17) and Th1 cells (30). We...
could assume that the available antiretroviral therapies may restore this balance, helping to reduce the inflammatory component.

Another explanation regarding the clinical stability of all patients reported is that antiretroviral medications used to suppress HIV replication, in theory, may suppress other viral pathogens implicated in MS, like Human Endogenous Retroviruses (HERVs) and herpes viruses (32-37).

**Conclusion**

In conclusion, our case report highlights the possible pathophysiological interaction between HIV and MS and the likelihood of a positive influence of HIV on the clinical course of MS, a hypothesis that needs to be further investigated. We also suggest that the probable beneficial effects of antiretroviral drugs on the progression of MS should be further explored as they could offer an alternative, apart from conventional, immunomodulatory MS therapy.

**Conflicts of Interest**

The Authors declare no conflicts of interest.

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