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CASE REPORT

Multiple sclerosis typical clinical and MRI findings in a patient with HIV infection

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Abstract
Background Multiple sclerosis (MS) is a demyelinating disease seldom included in the differential diagnosis of leukoencephalopathy in HIV-positive patients.
Methods We describe the clinical findings and laboratory results of a 43-year-old male with HIV infection and MS, and reviewed 11 more cases reported in the literature.
Results The first episode of MS occurred either during or after the recognition of the HIV infection except in the few cases reported in 1989. There has been a very strong male predominance. Age at onset was between 30 and 40 years old. The most common clinical course was relapsing and remitting. Most of the cases had a normal CD4+ cell count, usually exceeding 500 cells/mm^3. Despite that CD4+ cell counts were invariable high, all the patients had multiple tests to rule out opportunistic infections and HIV-associated illness. The clinical suspicion of MS was only considered after ruling out other opportunistic infections and was supported with brain imaging showing multiple white matter evanescent lesions, the presence of black holes, and a high myelin basic protein titer in the CSF.
Conclusions MS is usually considered late in patients with HIV. A typical MS course with suggestive MRI lesions and absence of severe immune suppression should suggest the diagnosis. It is possible that as with other MS patients, earlier initiation of specific treatments for MS will prevent the high burden of the disease and disability in these patients, but stronger evidence for specific recommendations remains to be obtained.

Keywords Multiple Sclerosis · HIV · Leukoencephalopathy

Background

The main causes of white matter lesions in HIV-infected patients are HIV encephalopathy (HIV-E) and progressive multifocal leukoencephalopathy (PML). Both occur with a higher degree of immune suppression, in later phases of the disease. The majority of other focal lesions also occur after severe immune suppression, and they correspond to opportunistic infections such as toxoplasmosis, primary central nervous system lymphoma, cytomegalovirus, or tuberculosis (Uriel et al. 2010).

Multiple sclerosis (MS) is an inflammatory disease of the myelin sheaths around the axons of the brain, leading to demyelination and a broad spectrum of neurological abnormalities. Demyelinating lesions occur particularly in the periventricular area of the brain or in the spinal cord white matter. Although much is known about the mechanisms involved in the process, the cause remains unknown. Theories include genetics, infection, vascular abnormalities, or environmental risk factors.

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MS is rarely considered a differential diagnosis in HIV-infected patients, despite the fact that MS-like syndromes have been well defined in some patients with HIV (Berger et al. 1989, 1992; Gray et al. 1991; García-Delange et al. 1995; Graber et al. 2000; Duran et al. 2004; Uriel et al. 2010). Prior to the availability of specific therapy for MS, clinicians did not necessarily move with readiness to establish the diagnosis in patients with subtle or transient manifestations, but with the advent of immunomodulating therapy, it has become more important to diagnose MS more effectively earlier on in the course of the illness (Fadil et al. 2007). We describe the classical clinical course and MRI lesions of MS in a patient with HIV infection and compare it to the cases in the literature.

Case presentation

A 43-year-old homosexual male was diagnosed HIV positive as part of a routine screen in 1996. He was started on lamivudine (3TC), stavudine (d4T) and efavirenz with a nadir CD4+ cell count of 205 cells/mm^3 and a viral load of 714,773 copies. After ARV treatment his CD4+ cell count increased to 586 cells/mm^3, and he achieved an undetectable viral load. Five years later, he developed an episode of dizziness, paresthesias in the left arm and leg, and weakness of the left arm. CD4+ cell count at that time was 908/mm^3. An MRI showed multiple T1 hypointense and T2/FLAIR hyperintense periventricular white matter lesions between 0.5 and 1.5 cm (Fig. 1a). As toxoplasma infection was suspected, he received treatment with pirimetamine and clindamycin with full recovery of his symptoms. One year later, he developed a new event of sudden vertigo and left side weakness. His CD4+ cell count at that time was 702 cells/mm^3. His MRI showed new periventricular white matter lesions (Fig. 1b). He received treatment with gabapentin and had a full spontaneous recovery. Another year later, he had a third neurological flair consisting of weakness and paresthesias of the right arm and leg. His MRI showed a new lesion in the right frontotemporal region (Fig. 1c). He did not receive any treatment and recovered spontaneously. Six months later, he developed a right cerebellar syndrome. His CD4+ cell count was 564 cells/mm^3, and the MRI showed a new periventricular and new infratentorial lesions (Fig. 2). A brain biopsy was performed which was non-diagnostic. Multiple CSF results in the search for infectious causes were negative, including negative cryptococcal antigen test and negative polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*, Cytomegalovirus, Herpes simplex virus, Epstein–Barr virus, *Toxoplasma gondii*, and JC virus. CSF VRDL was also negative. However, his CSF was positive for >5 well defined gamma oligoclonal bands, a low myelin basic protein of >6 μg/l (normal value <2.2 μg/l), total proteins of 49 mg/dl (15–45 mg/dl), high IgG synthesis in CSF of +11.2 mg/24 h (<0.66), and high IgG index in CSF of 0.80 (<0.66). He was started on immune modulatory treatment, and he has not presented further neurological episodes.

Discussion

Although several types of white matter lesions have been described in HIV-E including small perivascular focal rarefactions (Berger et al. 1992), the clinical manifestations exhibited in this case were inconsistent with that diagnosis. Evidence against it included the absence of cognitive, behavioral, or extrapyramidal abnormalities. PML was ruled out on the absence of significant immune suppression, the reversible neurological deficits, and failure to obtain a positive PCR JCV test on two occasions. Other opportunistic infections were aggressively searched for, and regardless of a high CD4+ cell count, a therapeutic trial against toxoplasmosis was initiated. Despite being a very common infection in our country, neurocysticercosis was not considered among the differential diagnosis, possibly because the radiological images were not suggestive. Immune reconstitution inflammatory syndrome (IRIS) was not considered in this case because the neurologic presentation occurred many years after ARV initiation and the patient did not have severe immune suppression at the time he began ARVs. Clinically definite remitting and relapsing MS was diagnosed because the patient fulfilled the Schumacher criteria (objective abnormalities in the neuro-

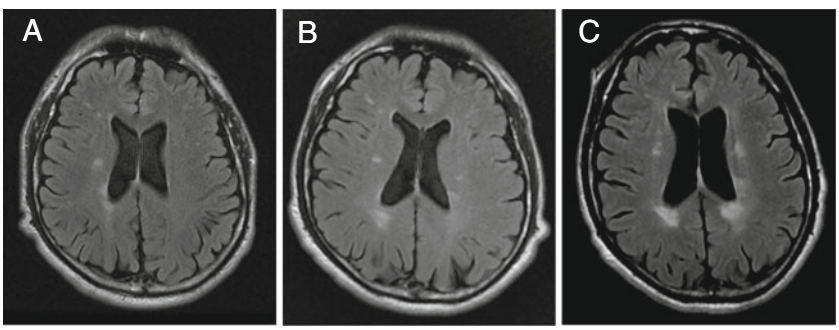

Fig. 1 MRI FLAIR-weighted image showing multiple periventricular hyperintense white matter lesions. As time passes, the lesions vary, but there is a trend toward increasing, a characteristic that in MS is known as *lesion burden*

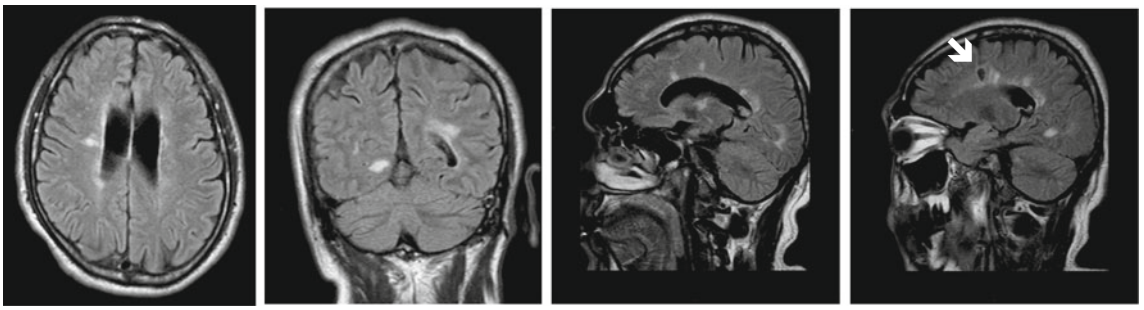

Fig. 2 Characterisitic MS periventricular white matter lesions along with a black hole (*arrow*). Last to appear on the MRI are the so called "black holes", which are irreversible, equivalent to axonal destruction and loss of brain substance

logical examination, two or more CNS parts involved, predominant white matter involvement, and two or more episodes, each lasting at least 24 h, and at least 1 month apart) (Schumacher et al. 1965). The presence of oligoclonal bands, elevated myelin basic protein and the characteristic periventricular white matter lesions on the MRI supported the diagnosis (McDonald et al. 2001).

The hallmark of MS is clinical recovery from neurological deficit followed by relapsing disease. Berger et al. (1989) reported seven patients with a neurological disease "clinically indistinguishable from MS occurring in association with seropositivity for HIV-1." Since then, only four more patients have been described in the literature with MS and HIV (Table 1). Three cases with a single tumefactive demyelinating lesion were recently described (Uriel et al. 2010); however, it remains to be seen if this is MS or a variant of the same disease, and therefore we did not included them in the analysis.

In most of the cases, MS was heralding the HIV diagnosis, either occurring during or after the recognition of the HIV infection. Five patients presented the first MS episode simultaneous to the HIV diagnosis and three

Table 1 Main clinical characteristics of patients

Case	Age (years)	Gender	Onset to HIV dx	Nadir CD4+ count (cells/mm^3)	CD4+ at first episode (cells/mm^3)	Number of episodes	AIDS related diagnosis
1 (Berger et al. 1989)	29	M	0	276	760	2	none
2 (Berger et al. 1989)	28	M	0	320	320	2	none
3 (Berger et al. 1989)	45	M	0	NA	NA	3	*P. carinni*[a]
4 (Berger et al. 1989)	26	M	−4 years	92	NA	6	Candidiasis High CMV serum titers
5 (Berger et al. 1989)	36	M	−5 years	NA	NA	2	AIDS (?)
6 (Berger et al. 1989)	28	M	−10 years	1,088	1,088	6	Herpes genitals, candida, CMV pneumonia
7 (Berger et al. 1989)	41	M	−18 years	12	12	3	Gram-negative pneumonia
8 (García-Delange et al. 1995)	66	M	0	1,300	1,300	3	None
9 (García-Delange et al. 1995)	42	M	0	NA	NA	1	None
10 (Berger et al. 1992)	33	M	0	NA	349	4	None
11 (Berger et al. 2009)	35	F	8	88	666	4	Herpes zoster
12 (Graber et al. 2000)	28	F	0	554	554	3	none
13 (Facchini et al. 2002)	8[b]	M	8y	NA	282	2	Recurrent URI[b] Lymphoid interstitial pneumonitis
14 (Duran et al. 2004)	32	M	2 m	210	425	1	None
15 (Nkoghe et al. 2008)	32	M	0	687	687	2	None
16	43	M	5y	205	908	3	None
Total	34.5 (8–66)			474 (12–1,300)	571 (12–1,300)	2.2 (1–6)	

M male, *F* female, *NA* not available, *URI* upper respiratory infections

[a] *P. carinni* infection was the cause of death of this patient 2 years after initial neurologic activity in 1987 without ARV treatment

[b] This patient acquired HIV at birth, thus the young age

patients presented symptoms 2 months and up to 8 years after the HIV diagnosis was performed. Four patients had the first MS episode before the HIV diagnosis, but all of them were described in 1989 (Berger et al. 1989), a time when diagnosing HIV was not common, and therefore they could also have had HIV before or during seroconversion. Mean CD4+ cell count at the first MS episode was high at 571 cells/mm^3. Only one patient had low CD4+ cell count, and was the one who had the longest period between the first MS episode and the HIV diagnosis (18 years). Interestingly, except one woman, all the other patients were men. Mean age at first MS episode was 34 years old, and the relapsing–remitting clinical form was the predominant clinical presentation. Risk factors are unknown, except for one case with associated Coxsackie B infection in the CNS (Berger et al. 2009). Berger et al. (1989, 1992) and Gray et al. (1991) described a clinical course worse than typical in MS. The other patients had a typical clinical course.

Like MS, HIV-E may be associated with discrete hyperintense signals in the white matter on T2-weighted MRI of the brain, elevated CSF immunoglobulins, and CSF oligoclonal bands. However, the elevation of myelin basic protein (MBP) in the CSF is distinctly unusual in HIV (Berger et al. 1989). Remarkably, none of the patients with advanced HIV-E or PML due to JCV infection display the chronic characteristic MS lesions called “black holes” in the MRI (Fig. 2).

Histopathologic findings in the white matter lesions of patients with MS are particularly different from the findings of HIV-E and PML. MS features comprise perivascular demyelination accompanied by phagocytic microglia and diminished numbers of oligodendrocytes. HIV-E pathology is characteristic for the presence multinucleated giant cells, microglial nodules and astrocytosis (Fadil et al. 2007). Histopathologic hallmarks of JCV PML include the triad of oligodendroglial inclusions, demyelination, and bizarre, atypical astrocytes (González-Duarte et al. 2009). In JCV PML, the foci of white matter demyelination may be found in the intracortical and subcortical white matter, surrounded by a large number of JCV-infected cells, whereas demyelination in MSis prominently subpial, with a greater density of lymphocytes in the rim immediately above the subpial lesions, suggesting a link to soluble mediators that diffuse from the subarachnoid or perivascular space (Moll et al. 2008). The degree of inflammation is also different between the three lesions. PML lesions include more inflammatory elements than HIV-E, but there is a relatively non-inflammatory environment in PML lesions when compared to the MS lesions (Moll et al. 2008).

The possible link between HIV and MS is intriguing. There has been some epidemiologic evidence linking MS to other viral infections, especially to Epstein–Barr virus (EBV), however the underling mechanism is elusive (Otto et al. 2011). About 90% of patients with MS show an elevated antibody index against one or more neurotropic viruses (Otto et al. 2011), although this is possibly due as part of a polyspecific intrathecal humoral immune response (Otto et al. 2011). Patients with HIV also show high intrathecal immunoactivation, up to the point that intrathecal immunoglobulin production can be measured even after years of effective HAART treatment and undetectable viral load (Eden et al. 2007). The intrathecal antibody response may be partly responsible in controlling the HIV infection, as it has been shown that the humoral response plays an active role in suppressing viral species in the CNS in experimental simian immunodeficiency virus (SIV) infection (Ryszhova et al. 2009).It is possible that this higher rate of immune activity in the CNS could be a contributing factor for the formation of MS lesions in some patients.

Alternatively, the effect of HIV-1 on specific subsets of lymphocytes such as the suppressor–inducer cells could be accountable of the neurologic disease (Berger et al. 1989). Chronic persistent cellular immune activity is one of the most important features of the HIV infection. There is a high interchange of T cells, monocytes and natural killer cells (NK), high levels of apoptosis of CD4+ and CD8+ cells, and high proinflammatory cytokine levels. Moreover, different CD4+ subtype losses occur through HIV infection. Cell-mediated immunity is also believed to be the most important component in the pathogenesis of MS. Among the observed changes in the immune system of the patients with MS is an abnormality of the functional activity of suppressor cells, with a subsequent defect in the suppressor/inducer cell system (Morimoto et al. 1989; Kieseier 2011).

Regardless of the mechanisms, the imbalance in the immune systems in the patients with HIV could prompt a CNS demyelinating disease of variable severity similar to the Guillain–Barré syndrome (GBS) described concomitant with HIV seroconversion prior to developing acquired immunodeficiency syndrome (AIDS) (Gray et al. 1991; Duran et al. 2004), or following immune reconstitution syndrome (Teo et al. 2007). The pathogenesis of GBS in these patients is based largely on the action of T cells, macrophages, and cytokines. A case series of GBS in HIV-infected patients suggested the role of T cell suppression in the triggering of GBS. This suppression, in addition to the actual HIV infection, may make the immune system prone to autoimmune attacks (Kieseier 2011).

In light of the prevalence of both MS and HIV infection it is surprising that there are so few cases reported. We do not think that MS is over or underrepresented in the HIV population, rather that it may occur in some patients and its relationship is overlooked or misguided by other HIV-related diseases. It would not be surprising that an increased polyspecific immune response in the CNS, in addition to a CD4+ suppressor subtype loss elicited by HIV infection,

could be responsible for the MS-like symptoms in patients with HIV infection and high CD4+ cell counts. However, we agree with other authors (Duran et al. 2004) that pure random coincidence associated with the prolonged survival rate now seen in these patients cannot be ruled out. Future studies such as HIV recognition by PCR in biopsy proven brain demyelinating lesions, and better CD4+ profile characterizations in these patients will clarify if the relationship of MS and HIV is casual or not. Unfortunately, decisions regarding treatment or follow-up recommendations for these patients are yet to come.

Conclusion

MS should be considered in the differential diagnosis in HIV-infected patients with white matter lesions and a clinical intermittent course. Absence of severe immune suppression may further suggest the diagnosis.

Disclosures The authors have nothing to disclose.

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