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Motor neuron disease in patients with HIV infection: Report of two cases and brief review of the literature

Paulo José Lorenzoni, Renata Dal-Prá Ducci, Giuliano Ohde Dalledone, Claudia Suemi Kamoi Kay, Sérgio Monteiro de Almeida, Lineu Cesar Werneck, Rosana Hermínia Scola*

Service of Neuromuscular Disorders, Division of Neurology, Department of Internal Medicine, Hospital de Clínicas, Universidade Federal do Paraná (UFPR), 80060-900, Curitiba, Brazil

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ABSTRACT

HIV-associated motor neuron disease (MND), or amyotrophic lateral sclerosis (ALS)-like syndrome associated with HIV infection, is a rare manifestation of HIV infection. HIV-associated MND has only been identified in few cases to date. We analysed two Brazilian patients with HIV infection who developed MND. The diagnosis of HIV infection was concomitant with diagnosis of MND in one patient and it occurred eight years before the MND symptoms in another patient. The manifestation of MND in our patients with HIV infection was similar to classic ALS. The antiretroviral therapy improves their HIV infection. However, slow progression of MND occurred in the two patients despite their antiretroviral therapy or HIV viral load (undetectable). We revised the international literature (PubMed database) of the patients reported with MND and HIV infection.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease (MND) in adults [1–3]. ALS is characterized as progressive neurodegenerative disease with upper and lower motor neuron degeneration [2,3]. Although several genetic forms have been identified, the underlying etiology of the majority of cases remains unknown [1,3].

An ALS-like syndrome may also occur in some cases where neurodegeneration of motor neurons in the brain and spinal cord is due to another disease. In recent years, ALS-like syndrome has been reported to be associated with human immunodeficiency virus (HIV) infection [4–19]. However, because its characteristics are different from classical ALS, the term “HIV-associated motor neuron disease” has been used to distinguish this rare manifestation of HIV infection [5].

In this study, we reported two Brazilian patients with HIV infection who developed MND and revised the international literature.

2. Methods

We analysed 104 patients with ALS diagnosis admitted from January 2006 to January 2016 at the out-patient clinic of the Hospital de Clínicas of Universidade Federal do Paraná (Curitiba, Brazil). We included patients in our study that presented with an ALS diagnosis according the “El Escorial” diagnostic criteria, positive HIV serology; and concomitance of ALS and HIV infection. Relevant data, including age, gender, the time of progression of both diseases, the course of both diseases, clinical manifestation, disease management, central nervous system (CNS) penetration (CPE) ranking of the antiretroviral (ARV) therapy [20], laboratory data and electromyography features, were collected. All studies were performed in accordance with ethical principles after obtaining patient consent.

We reviewed the international literature (PubMed database) after patients reported with MND and HIV infection. Relevant data were collected, including gender, age at diagnosis of HIV infection, age at MND manifestation, laboratory data (CD4 cells count and HIV viral load), MND course (progression, improvement or stable), and the clinical follow-up (time and outcome). The patients were categorized in two groups according to diagnosis of HIV infection: simultaneously to MND manifestation or previous to MND manifestation.

3. Results

We describe the main characteristics of the two patients (1.9%) who fulfilled all the clinical criteria. Table 1 compares the main data and therapy in the two patients. We excluded the remaining 102 patients

* Corresponding author.
E-mail address: rosana.scola@hc.ufpr.br (R.H. Scola).

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Table 1
Age at onset, ARV therapy and MND course of HIV-associated motor neuron disease in our patients.

Case	1	2
Gender	Male	Male
Age at MND onset, y	60	45
Age at HIV serology, y	61	37
Age at AIDS, y	61	44
ARV therapy at MND onset	No	ATV, TDF and 3TC (CPE ranking: 5)
ARV therapy after MND diagnosis	EFV, AZT and 3TC (CPE ranking: 9)	RAL, TDF and 3TC (CPE ranking: 6)
ALS course	Progression / Died	Progression / Alive

HIV: human immunodeficiency virus; MND: motor neuron disease; ARV: antiretroviral; CPE: CNS-penetration efficacy; ATV: atazanavir; AZT: zidovudine; 3TC: lamivudine; EFV: efavirenz; TDF: tenofovir; RAL: raltegravir.

with ALS who presented with negative HIV serology.

3.1. Case 1

Case 1 was a 60 year old man who developed progressive speech difficulties and left lower limb weakness associated with fasciculation. Six months later, his lower and upper limbs were committed and he has also developed dysphagia. He was former smoker and drinker. At 61 years old, neurological examination revealed atrophy and fasciculation in the tongue, diffuse weakness in the upper and lower limbs associated with atrophy, fasciculation and hyperreflexia. The initial diagnosis was ALS, but initial investigation at an in-patient clinic showed the following results: positive HIV serology, a CD4 count of 250 cells/mm^3 and viral load of 40.636 copies/mm^3; cerebral spinal fluid (CSF) analysis showing 25 cells/mm^3 (94% of monomorphonuclear) and protein analysis showing 83 mg/dL; acute denervation with fasciculation, fibrillations and positive waves in several muscles in the bulbar, cervical, thoracic and lumbar segments on needle electromyography; and normal nerve conduction studies. Other investigations, such as brain and spinal MRI, thorax CT scan, abdomen ultrasonography and upper gastrointestinal endoscopy, were all normal. The diagnosis was ALS and AIDS. The initial management was carried out with riluzole, zidovudine (AZT), lamivudine (3TC) and efavirenz (EFV) (CPE ranking: 9) which was started one year after the onset of neurological symptoms. One month later, combined ARV therapy resulted in undetectable HIV viral load but the CD4 count was 245 cells/mm3. He presented with slow progression of weakness and atrophy, mainly in lower limbs and hands, associated with anorexia and depression. He died due to respiratory failure 2 years after his ALS diagnosis.

3.2. Case 2

Case 2 was a man who had detectable levels of HIV at 37 year old. At age 44 year old, AIDS was diagnosed when the viral load was greater than 500,000 and the CD4 count was 341 cells/mm^3. Combined ARV therapy was added with AZT, 3TC and EFV (CPE ranking: 9), but the management was changed to tenofovir (TDF), 3TC and EFV (CPE ranking: 6) after adverse events related to AZT. At 45 years old, he showed muscular weakness in the left upper limb (especially in distal segment) associated with fasciculation, which progressively became diffuse in the following 2 years. There were no relatives with similar symptoms. At 47 years old, neurological examination revealed fasciculation in the tongue, upper and lower limbs; asymmetrical weakness in the upper limb paresis (left > right); generalized muscular atrophy (distal > proximal); diffuse hyperreflexia; and Babinski and Hoffman's signs bilaterally. At that time, his ARV therapy was atazanavir (ATV), TDF and 3TC (CPE ranking: 5). The initial diagnosis was ALS in an HIV-infected patient, and investigation yielded the following results: undetectable HIV viral load and normal CD4 count (893 cells/mm^3); acute denervation with fasciculation, fibrillations and positive waves in muscles of the bulbar, cervical, thoracic and lumbar segments revealed by needle electromyography; normal nerve conduction studies; and normal brain and spine MRI. The HIV infection therapy was changed to raltegravir (RAL), TDF and 3TC (CPE ranking: 6) which occurred 2 years after the onset of neurological symptoms. The patient refused the ALS treatment with riluzole. He presented with slow progression of weakness and atrophy 6 years after the ALS diagnosis.

4. Literature review

We found 37 patients reported in the international literature (PubMed database) with HIV infection and MND manifestation, but four patients were excluded because they did not have full descriptions at the time that HIV infection was diagnosed [5–19].

MND manifestation was simultaneous to HIV diagnosis in 11 patients, but four patients were excluded due to incomplete clinical and/or laboratory data [9,15–17,19]. MND manifestation occurred after HIV infection in 22 patients, but two patients were excluded due to incomplete clinical and/or laboratory data [5–14].

HIV infection was simultaneous to MND manifestation in six male and one female (Table 2). HIV infection was previous to MND manifestation in 18 males and two females (Table 2).

The age of the diagnosis of the HIV infection was similar between MND patients with simultaneous or previous HIV infection (Table 2). In patients with previous HIV infection, the mean time of the MND onset was 8 years after HIV infection (Table 2).

The CD4 cell count was similar between both groups, but the HIV load was greater in the group recently diagnosed with HIV infection (Table 2).

The proportion of patients with progressive MND was greater when MND and HIV infection were simultaneous (Table 2). In addition, only patients previously diagnosed with HIV infection had improvement of MND (Table 2).

The time of follow-up was greater in patients previously diagnosed with an HIV infection than in patients whose diagnosis of MND was simultaneous to HIV infection (Table 2). The proportion of patients who died was similar between both groups.

Table 2 shows the main characteristics of patients previously reported in the international literature (PubMed database) [5–19].

5. Discussion

In this case series, we present two patients with HIV infection who developed motor neuron disease involving both upper and lower motor neurons. The diagnosis of HIV infection occurred simultaneously to the ALS manifestation in one patient and previously in another. In our literature review, MND manifestation was described after HIV infection in almost 75% of cases [5–19]. There is no definitive diagnostic test for ALS, and confirmation of diagnosis is based on clinical findings, electromyography results, and exclusion of other diagnosis. Both patients had signs and symptoms of upper and lower motor neuron involvement, and electromyography findings were consistent with MND by "El Escorial" criteria.

HIV-associated NMD was first described in 1985 [8], but has been rarely reported since then [4–19]. The prevalence of ALS is estimated to be almost 100 times greater in patients with HIV infection (3.5 cases per 1000 patients) [6] than in the general population (4–6 cases per 100,000) [1]. In our study of 104 patients with ALS, the frequency of HIV-associated MND was estimated to be 1.9%, which is similar to the literature.

As an ALS-like syndrome, HIV-associated MND presents neurologic manifestations that are indistinguishable from "classic ALS", except that it has an early onset and beneficial response to ARV therapy in some patients [8–10,14,16]. Its course can be fast in some patients, sometimes only weeks or months [8,9,21]. HIV-associated MND is