

PARKINSONISM AND AIDS

A clinical comparative study before and after HAART

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Abstract – In 2002, after analyzing 28 HIV-positive patients with movement disorders we emphasized the decreasing not only of Parkinsonism but also of other involuntary movements in HIV patients in the last few years. The objective of this study is to compare the clinical results between HIV-positive patients with Parkinsonism before and after HAART. In 14 years (1986–1999) 2,460 HIV-positive patients were seen in our Hospital 14 (0.6%) of which presented with Parkinsonism. Eight years after (2000–2007) 970 HIV positive patients were seen and only two (0.2%) had Parkinsonism. We conclude that after the introduction of HAART there was an evident decrease in AIDS-related Parkinsonism.

KEY WORDS: Parkinsonism, AIDS, HIV, antiretrovirals.

Parkinsonismo e AIDS: estudo clínico comparativo antes e após o esquema HAART

Resumo – No ano de 2002, após analisarmos 28 pacientes HIV-positivos que apresentavam distúrbios do movimento, enfatizamos o declínio, não só do parkinsonismo, como também de outros movimentos involuntários em pacientes infectados pelo HIV nos últimos anos. O objetivo deste estudo é comparar os resultados clínicos entre pacientes HIV-positivos com parkinsonismo antes e depois da introdução do esquema HAART. Em 14 anos (1986–1999), 2.460 pacientes HIV-positivos foram avaliados em nosso Hospital dos quais 14 (0,6%) apresentaram parkinsonismo. Nos oito anos seguintes (2000–2007), 970 pacientes HIV-positivos foram avaliados e somente dois (0,2%) tinham parkinsonismo. Concluímos que após a introdução do esquema HAART houve evidente declínio do parkinsonismo secundário à AIDS.

PALAVRAS-CHAVE: Parkinsonismo, AIDS, HIV, antiretrovirais.

Since 1986 our hospital became a reference center for diagnosis and treatment of HIV-positive patients. The highly active antiretroviral therapy (HAART) was only introduced in 2000. In an earlier study¹, after analyzing 28 HIV-positive patients of the pre-HAART era with movement disorders we started to observe the decrease not only in Parkinsonism but also in other involuntary movements in HIV patients in the last few years.

We then suggested this fact was related to the introduction of HAART. Then we speculated that in the near future we would see not only a decline in many opportunistic infections but also in the neurological complications and in the mortality of the HIV patients.

The aim of this study is to analyze the clinical com-

parative results between HIV-positive patients with Parkinsonism before and after HAART.

METHOD

The period between 1986 and 1999 was defined as the pre-HAART era and after 2000 the post-HAART era.

The clinical diagnosis of Parkinsonism was made based on the presence of at least two of the following signs and symptoms: rest tremor, bradikinesia, rigidity and postural instability. The Hoehn and Yahr modified (H&Y) scale was used to follow-up the disease progress. All patients underwent either computerized tomography (CT) or magnetic resonance imaging (MRI) and some had cerebrospinal fluid (CSF) examination.

The AIDS diagnosis was based on the Center of Disease Con-

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trol (CDC) / World Health Organization (WHO) classification system². The time of HIV infection was calculated based on the date of the Western-Blot confirmation.

This study was approved by the ethics committee of the Universidade Federal do Rio de Janeiro.

RESULTS

Pre-HAART era

In 14 years (1986-1999) 2,460 HIV-positive patients were seen in our Hospital, 14 (0.6%) of them with Parkinsonism. Eleven were males and three females. Twelve were Caucasian and two African-Brazilians. The mean age at the onset of the Parkinsonian symptoms was 37.2 years (range 25 to 63). According to the high-risk category, five were homosexual, three bisexual, two intravenous drug users (IDU) and one had a blood transfusion. Four patients did not show any identifiable risk. Tremor was seen in eight (57.2%) as the initial symptom. At the first examination patients had a mean score in the H&Y scale of 2.5 (range from 1 to 5). All patients underwent CT scans. Seven (50%) showed ex-vacuum hydrocephalus due to cortical-subcortical atrophy. One patient had a hypodense area with mass effect suggestive of toxoplasmosis of the right basal ganglia. One had an enhancing lesion in the midbrain at the T1 weighted MRI, which was correlated clinically with a homolateral ophthalmoplegia and contralateral hemiparkinsonism (Benedikt syndrome). The parkinsonism was

probably secondary to HIV in 12, to metoclopramide in one and to neurotoxoplasmosis in another one. The mean time from the HIV diagnostic to the onset of the symptoms was five months. Only five out of nine patients that used levodopa had mild improvement. In eight patients the mean time from the onset of parkinsonism and death was five months (Table).

Post-HAART era

In the last eight years (2000 - 2007) 970 HIV positive patients were seen and only two (0.2%) had Parkinsonism and are described below.

Case 1

A 60-year-old, African-Brazilian bisexual man presented in March 2000 with oral candidiasis and *Pneumocystis carinii* pneumonia. An ELISA for HIV was positive. Three months later he was started on zidovudine, lamivudine and nelfinavir. Initially the viral load was 450,000 copies/mL. It was necessary to change drugs many times because of his non-adherent behavior to HAART. As a result the viral load and the CD4 levels varied greatly (from 450,000 to 120 copies/mL and from 38 to 189/ mm³, respectively). One year later, on irregular use of HAART, he presented a rest tremor on the left arm. On the neurological examination there was bradikinesia and rigidity on the right arm besides the rest tremor. The brain CT was normal.

Table. Comparative results between HIV-positive patients before and after HAART.

	Before	After
Gender	M=11 F=3	M=1 F=1
Ethnia	C=12 AB=2	AB=2
Age of onset of Parkinsonism (years)	mean=37.2 (25-63)	mean=62.5 (55-70)
Risk behaviour	homosexual=5 bisexual=3 IDU=2 blood transfusion=1 unknown=4	bisexual=1 unknown=1
Brain CT / MRI	ex-vacum atrophy=7 BG toxoplasmosis=1 midbrain toxoplasmosis=1	atrophy=1
Time between HIV and Parkinsonism (months)	mean=5	mean=9
Improvement with dopaminergic drugs	mild=5	marked=2
Time of Parkinsonism	mean=5 months to death	mean=71.5 months
Etiology	HIV=12 metochlopramide=1 toxoplasmosis=1	HIV ? / PD ?=2

M: male; F: female; C: Caucasian; AB: African-Brazilian; IDU: intravenous drug user; CT: computerized tomography; MRI: magnetic resonance imaging; BG: basal ganglia; HIV: human immunodeficiency virus; PD: Parkinson's disease.

Levodopa (250 mg/day) and amantadine (100 mg/day) reduced the Parkinsonian symptoms. Atrial fibrillation and tuberculosis pneumonia were treated five and six years later, respectively. At that time, he noted rest tremor on the right arm. Increasing the levodopa (375 mg/day) and amantadine (200 mg/day) doses resulted in further improvement. At the end of 2007 the patient was clinically stable with the use of HAART as well as levodopa and amantadine.

Case 2

A 73-year-old African-Brazilian woman presented with ophthalmic *Herpes zoster* on the left side, in October 2003. An ELISA for HIV was positive on two separate occasions although there was no known history of risk behavior for HIV. At that time the viral load was 33,000 copies/mL and CD4 levels 404/mm³. She was then started on zidovudine, lamivudine and efavirenz with good adherence to the treatment. Rest tremor on the right hand as well as facial hypomimia and upper right limb bradikinesia were observed three months later. Piribedil 100 mg/day has reduced the tremor. Two years later, increased rigidity was noted involving the four limbs asymmetrically. The brain MRI was normal. After four months of HAART the viral load decreased from 33,000 copies/mL to less than 80 copies/mL, which is regarded as undetectable and remained unchanged until the end of 2007. The CD4 levels ranged from 251 to 404/mm³. No opportunistic infection was observed in those years.

The Table shows the comparison between the two groups before and after HAART detailing demographic data, age of onset of Parkinsonism, risk behavior, brain imaging, etiology of Parkinsonism, time from HIV diagnosis to Parkinsonism, improvement with levodopa and the duration of Parkinsonism.

DISCUSSION

Since the year 2000, the decline of the number of patients with HIV-related movement disorders was observed in our Hospital, mainly on Parkinsonian patients, probably due to the introduction of HAART¹. This fact has also been observed in the literature³⁻⁶.

Currently HAART consists of four classes of drugs: nucleoside reverse transcriptase inhibitors and nucleotide analogs (NRTIs) (Lamivudine, Zalcitabine, Zidovudine, Didanosine, Tenofovir, Stavudine and Abacavir); non-nucleoside reverse transcriptase inhibitors (NNRTIs) (Delavirdine, Efavirenz and Nevirapine); protease inhibitors (PIs) (Indinavir, Saquinavir, Ritonavir, Atazanavir and Nelfinavir) and fusion inhibitors⁷. All initial regimens consist of two NRTIs, combined with either PI or NNRTI⁸.

The clinical comparative analysis of HIV-positive parkinsonian patients before and after the introduction of

HAART depicted, in our study, the decline of its incidence, from 14 (0.6%) to 2 (0.2%) patients.

Regarding the age at Parkinsonism onset, we noticed that patients had late-onset (>50 years) in the post-HAART era when compared with the pre-era (<40 years). The literature has emphasized longer life span of these patients and we are currently seeing HIV-positive patients with more advanced age who are at risk to develop co-morbid diseases such as degenerative Parkinsonism⁹.

The mean time between the HIV diagnosis and Parkinsonism onset increased from five to nine months showing a delay in motor symptoms onset in the post-HAART era.

Concerning the response to dopaminergic drugs from nine patients of the pre-HAART era five had only mild improvement; while in the post-HAART era both patients showed marked improvement, one to levodopa and the other one to dopaminergic agonist (piribedil).

The mean time between the onset of parkinsonism and death was only 5 months before HAART, also seen in the study by Arendt et al, in 1994¹⁰; whereas the two post-HAART patients are alive after 71.5 months. These observations showed the severity and the poor prognosis of the HIV-related Parkinsonism in the pre-HAART era and suggested that not only has HAART raised the life span but also lessened the speed of symptoms progression.

According to the etiology of Parkinsonism in the pre-HAART era, we could only establish a clear cause in two patients: one due to high doses of metoclopramide and another one to toxoplasmosis of the midbrain. In the remaining 12 patients there was no clear association with any infectious, neoplastic, vascular or drug-related cause. Subsequently we hypothesize that the signs and symptoms in these patients were related to the HIV itself. However, we cannot be certain if our two patients in the post-HAART era had Parkinson's disease or AIDS-related Parkinsonism. Supporting the Parkinson's disease diagnosis we have the age of onset (both patients had late-onset Parkinsonism); the slow onset and progression of the symptoms; marked improvement to dopaminergic drugs and no significant findings on neuroimaging. On the other hand, the only feature that corroborated the AIDS-related Parkinsonism diagnosis is the HIV-positive test shortly before the onset of the motor symptoms. The above elements suggest more likelihood of Parkinson's disease than AIDS-related Parkinsonism.

In conclusion, whatever the Parkinsonism etiology of the last two patients, our clinical comparative results showed that there is no doubt about the decline in the number of HIV-related parkinsonian patients in the post-HAART era.

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