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Short communication

Cerebellar degeneration and progressive ataxia associated with HIV-virus infection

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ABSTRACT

Introduction: The spectrum of neurologic disorders associated with HIV infection is very broad, resulting from direct virus invasion, opportunistic infections, malignancies and toxic effects of drugs.
Methods: Among a large cohort of ataxia patients (N = 1050) evaluated between 2008 and 2017, we detected four patients with HIV-infection who developed a pure progressive cerebellar ataxia syndrome combined with cerebellar atrophy.
Results: Adverse drug effects, opportunistic infections and malignancies as well as immune-reconstitution syndrome were ruled out based on history and laboratory data. The exact pathophysiological mechanisms of ataxia in HIV patients is not very clear, but seems to be immune-mediated or a direct neurotoxic virus effect leading to apoptosis of Purkinje and granular cells.
Conclusion: HIV infection should be investigated in adult patients with undetermined sporadic progressive pure ataxia with cerebellar atrophy.

1. Introduction

The spectrum of neurologic disorders associated with human immunodeficiency virus (HIV) is very broad. It can be divided into those that result from direct HIV infection, opportunistic infections of the nervous system, primary central nervous system lymphoma and other malignancies, toxic effects of therapies, and others [1]. The common neurodegenerative conditions which include HIV virus as a trigger include HIV-dementia complex and amyotrophic lateral sclerosis (ALS) [2,3]. Although there are some case reports of HIV-associated isolated cerebellar syndrome in the absence of identifiable opportunistic infectious, toxic or neoplastic agents, it is not usually considered the cause of progressive ataxia and cerebellar degeneration [4]. In this article, we describe a case series of four patients with cerebellar degeneration associated with HIV infection.

2. Methods

A large cohort of ataxia patients (N = 1050) was evaluated from 2008 to 2017 in order to determine the etiology of the ataxia. This sample included several causes of ataxias such as hereditary ataxias and sporadic ataxias. From this sample, four patients were identified as presenting progressive ataxia, cerebellar atrophy and positive test for HIV. Other secondary and neurodegenerative (such as multiple system atrophy) causes and most common hereditary ataxias (such as Friedreich and spinocerebellar ataxias) were ruled out. All four patients with HIV had a progressive pure cerebellar ataxia syndrome. Opportunistic infections or neoplasms that might justify the cerebellar involvement were ruled out based on history, laboratory and imaging data. Also, known HIV patients that

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presented with acute ataxia were not included in this series. All four patients described herein underwent duplicate PCR (blood, cerebrospinal fluid and urine) and all were negative for JC virus. We did not identify other patients with different forms of ataxia (hereditary or not) that presented with HIV infection, but HIV was tested only in patients with undetermined or sporadic ataxias. Table 1 summarizes the clinical features, brain imaging, medication and immunological data of each patient with HIV and cerebellar degeneration described in detail in the sequence of this paper.

3. Case reports

3.1. Case 1

A 44-year-old previously healthy woman presented with a one-year history of gait impairment. At the time, she was being treated for depression with quetiapine, fluoxetine and amytriptiline. She had no history of alcoholism or smoking habit, neither she had a family history of similar symptoms. Examination showed cerebellar ataxia, dysmetria, dysdiadochokinesia, dysarthria and slowed saccadic eye movements with nystagmus (**Video**). Initial brain MRI scan was normal. Routine laboratory studies, including liver, renal and thyroid functions were unremarkable. Vitamins and alpha-fetoprotein levels were normal. Serological tests for syphilis, anti-GAD ataxia, Celiac disease and rheumatologic diseases were negative. On a follow-up consultation, her ataxic symptoms worsened and she developed oral candidiasis and dysphagia leading us to suspect of HIV which was further confirmed (CD4 count was of 65 cells/mm^3, RNA viral load count was of 24880 copies/mL). Further serological tests for cytomegalovirus, herpes-simplex virus, toxoplasmosis and Epstein-Barr virus were all IgM negative. New brain MRI imaging revealed mild cerebellar atrophy (Fig. 1A). Cerebrospinal fluid examination (CSF) revealed mildly raised protein levels (51.9 mg/dL) with normal cell count (3.4 cells/mm^3) and glucose level (40 mg/dL). She was treated with highly active antiretroviral therapy (HAART), tenofovir, efavirenz and lamivudine, started upon confirmation of HIV, buspirone 10 mg daily and sulphametoxazol and trimethoprim. On a follow-up visit six months later, she had a mild improvement of the ataxia.

3.2. Case 2

A 47-year-old man presented with a 10-year-history of mild appendicular incoordination, dysarthria and gait ataxia. It slowly progressed and led to investigation due to worsening for the last year. He was unaware of other medical comorbidities and family history of ataxia. There was no alcoholism or drug use. His neurological exam disclosed bilateral dysmetria and dysdiadochokinesia and an ataxic gait (**Video**). He underwent an extensive laboratory investigation and all came out normal: routine laboratory studies, including liver, renal and thyroid functions, vitamins B12 and E, albumin, lactate and alpha-fetoprotein. Serological tests for syphilis, hepatitis, anti-GAD ataxia, Celiac disease and rheumatologic diseases were negative. Friedreich's ataxia and SCA gene panel were negative. HIV came out positive (CD4 cell count 827 cells/mm^3; RNA viral load 2885 copies/mL) three years ago. HAART (tenofovir, efavirenz and lamivudine) was started, but there was no improvement in gait. Further serological tests for cytomegalovirus, herpes-simplex virus, toxoplasmosis and Epstein-Barr virus were all IgM negative. Brain MRI disclosed global cerebellar atrophy and mild brainstem atrophy (Fig. 1B). He was undergoing motor rehabilitation.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.04.007.

3.3. Case 3

A 54-year-old woman diagnosed with HIV/SIDA since 1998 with CD4 cell count of 483 cells/mm^3 and undetectable RNA viral load presented with tremors, dysarthria and poor upper-limb coordination and slowly progressive gait ataxia ten years after the diagnosis of HIV. She was under treatment (HAART) since the diagnosis, the latest one comprising lamivudine, tenofovir and lopinavir/ritonavir. Past medical history of pulmonary tuberculosis treated 20 years ago and polyneuropathy presumably associated with the virus. Neurological examination showed appendicular and truncal ataxia combined with gait ataxia and hyporreflexia in the lowerlimbs (**Video**). Brain MRI showed severe cerebellar and mild brainstem atrophies (Fig. 1C). Routine laboratory studies, including liver, renal and thyroid functions were unremarkable. Vitamins and alpha-fetoprotein levels were normal. Serological tests for syphilis, anti-GAD ataxia, Celiac disease and rheumatologic diseases were negative. Further serological tests for cytomegalovirus, herpes-simplex virus, toxoplasmosis and Epstein-Barr virus were all IgM negative. HAART therapy was ruled out for more than one, considering a possible neurotoxicity, but no improvement was observed in ataxia progression. She started a motor rehabilitation program, but no improvement was observed.

3.4. Case 4

A 34-year-old woman known to have HIV infection for four years presented with a 18-month history of gait and speech impairment. She was under HAART therapy (atazanavir, ritonavir,

Table 1
Detailed clinical and neuroimaging features of the four patients with HIV and cerebellar ataxia.

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Female	Male	Female	Female
Age (years)	44	47	54	35
Age at onset (years) of ataxia	42	37	45	33
Age at HIV diagnosis	44	47	34	30
Pattern of ataxia	AA > AP	AA > AP	AA > AP	AA > AP
Axonal neuropathy	No	No	Yes	No
Speech disturbance	Dysarthria	Dysarthria	Dysarthria	Dysarthria
Oculomotor abnormalities	Slow saccade and nystagmus	Nystagmus	Nystagmus	Nystagmus
Cognitive and behavior symptoms	Absent	Absent	Absent	Absent
Neuroimaging findings	CA	CA	CA	CA
PCR for JC virus (Blood, CSF and urine)	Negative	Negative	Negative	Negative
HAART	Yes (started after ataxia)	Yes (stopped, but no improvement)	Yes (started after ataxia)	Yes (stopped, but no improvement)
CD4	65 cells/mm^3	827 cells/mm^3	483 cells/mm^3	169 cells/mm^3
Viral load	24880 copies/mL	2885 copies/mL	0 copies/mL	0 copies/mL

AA: axial ataxia; AP: appendicular ataxia; DTR: deep tendon reflexes; CA: cerebellar atrophy.

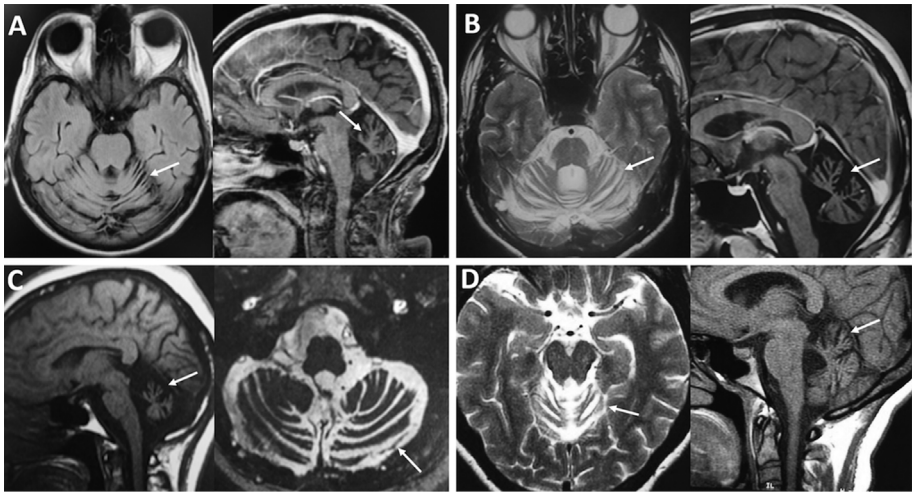

Fig. 1. A) *Patient 1:* Axial FLAIR-weighted and sagittal T1 brain MRI show global cerebellar atrophy (white arrows). B) *Patient 2:* Axial T2-weighted and sagittal T1 MRI demonstrate cerebellar and brainstem atrophy (white arrows). C) *Patient 3:* Sagittal T1 and T2-weighted and MRI demonstrate cerebellar and brainstem atrophy (white arrows). D) *Patient 4:* Axial T2-weighted and sagittal T1 MRI disclose pure cerebellar atrophy (white arrows).

lamivudine and tenofovir) since the diagnosis and prophylactic therapy with sulphamethoxazole-trimetoprim. Her latest CD4 cell count was of 169 cells/mm^3 with undetectable RNA viral load count. She initially complained of difficulty in walking in a straight line causing imbalance and falls, followed by dizziness and occasional vomiting. Neurologic examination revealed cerebellar ataxia, dysarthria and nystagmus (**Video**). There were no family history nor alcohol or drug habit. Brain MRI showed marked vermian atrophy (Fig. 1D). Routine laboratory studies, including vitamins, liver, renal and thyroid functions were unremarkable. Serological tests for syphilis, anti-GAD ataxia, Celiac disease and rheumatologic diseases were negative. IgM tests for cytomegalovirus, herpes-simplex virus, toxoplasmosis and Epstein-Barr virus were negative. CSF analysis was normal. Motor rehabilitation was started with poor improvement.

4. Discussion

Patients with adult onset non-familial progressive ataxia are classified in sporadic ataxia group. There are several diseases that may manifest with sporadic ataxia: toxic causes, immune-mediated ataxias, vitamin deficiency, infectious diseases, degenerative disorders and even genetic conditions. Considering heterogeneity in the clinical spectrum of sporadic ataxias, the correct diagnosis remains a clinical challenge. Although HIV may cause ataxia related to opportunistic infections, progressive ataxia caused by HIV virus is very unusual [5].

Viral infections, particularly due to HIV, have played an important role in neurodegeneration [6]. In HIV-dementia complex, axonal damage and diffuse neuronal loss occur as a result of apoptotic process [2]. And in ALS related with HIV, it is postulated that selective impairment of the motor neurons occurs due to neurotoxic viral proteins and cytokines. Interestingly, ALS may occur at any stage of HIV infection [3]. Other progressive neurological conditions related to HIV include axonal neuropathy, myelopathy and myopathy [6]. Although an inflammatory or autoimmune process is also postulated, corticosteroids and immunoglobulin failed to show a benefit in HIV associated ALS, which reinforces the theory of a neurodegenerative process [3]. In the four patients reported in this series, considering the progressive worsening and cerebellar atrophy, suggesting a degenerative process, we decided not to use intravenous human immunoglobulin.

Some few reports have demonstrated the relationship between progressive ataxia and cerebellar degeneration in HIV patients. The exact pathophysiological mechanisms of ataxia in HIV patients is not very clear but seems to be autoimmune-mediated or a direct neurotoxic virus effect leading to apoptosis of Purkinje and granular cells [4,7]. Anatomical and pathological studies have demonstrated a degeneration of the cerebellar cell layer and axonal swellings in the brainstem and spinal cord, but no evidence of infection, which reinforces the idea of a neurodegenerative process [7].

JC virus infection may cause subacute ataxia and must be ruled out [1]. Although our patients had a negative JC virus PCR, we could not rule out the JC-virus associated granule cell neuronopathy, a restricted gray-matter involvement by the JC virus, only diagnosed via brain biopsy. In an interesting study, 40 patients with HIV infection were evaluated as for loss of balance, and these findings were correlated with pontocerebellar abnormalities through brain imaging, suggesting a pontocerebellar tract impairment [8].

Although some studies have demonstrated that antiretroviral may reduce neurodegeneration in HIV infection [9], our four patients had an inexorable progression of the cerebellar symptoms, despite HIV therapy. Also, we had no evidence to consider that ataxia symptoms were caused by HAART or immune-reconstitution syndrome. Of note, one of our patients (patient 3) had an axonal neuropathy, also attributed to HIV or the side effects of HAART. Indeed, this patient was being treated with nucleoside reverse transcriptase inhibitors which may lead to a mitochondrial toxicity culminating in distal symmetric polyneuropathy, the most common neurotoxicity secondary to HAART.

In conclusion, HIV infection should be investigated in adult patients with undetermined sporadic progressive pure ataxia and cerebellar atrophy. Although rare, this condition might have been misdiagnosed or underreported because physicians do not usually link HIV to a cause of pure progressive cerebellar syndrome. Pathophysiological mechanisms may involve cerebellar degeneration instead of autoimmune or medication toxic effects, similar to neurodegeneration observed in ALS and HIV-dementia complex.

Authors' roles

1. Case report project: A. Conception, B. Organization, C. Execution;

2. Genetic testing: A. Conception, B. Execution;
3. Manuscript: A. Writing of the first draft, B. Review and Critique.

Pedroso, JL: 1A, 1B, 1C, 3A, 3B (Nothing to disclose).
Vale, TC: 1A, 1B, 1C, 3A, 3B (Nothing to disclose).
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Ribas, G: 1A, 3A, 3B (Nothing to disclose).
Kristochik, JCG: 1A, 3A, 3B (Nothing to disclose).
Germiniani FMB: 1C, 3B (Nothing to disclose).
Fink, MCDS: 1A, 3A, 3B (Nothing to disclose).
Oliveira, ACP: 1A, 3A, 3B (Nothing to disclose).
Teive, HAG: 1A, 1B, 3A, 3B (Nothing to disclose).
Barsottini, OG: 1A, 1B, 1C, 3A, 3B (Nothing to disclose).

Conflicts of interest

We have no conflict of interest relevant to this work.

Financial disclosure

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The authors declare that there are no additional disclosures to report.

Ethical statement

Full consent was obtained from the patient for the case report publication. Authors have read the Journal's Ethical Publication Guidelines.

Patients consent

Patients have consented to the publication of the videos accompanying this manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.04.007.

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