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Lateral amyotrophic sclerosis-like onset after combined antiretroviral treatment initiation

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ABSTRACT

Motor neuron disease (MND) have an incidence of 2 in 100 000 persons, resulting in the death of 1 in every 500 people affected. The most common disease in MND spectrum is amyotrophic lateral sclerosis (ALS). We describe the case of an ALS-like syndrome in a HIV patient.

This case report presents a 38 years old male from Peru with HIV who after 2 months of combined antiretroviral treatment (cART) initiation was admitted to the hospital for spastic paraplegia. On his first admission, rapid plasma reagent (RPR) was positive and he was treated for neurosyphilis and discharged. Nevertheless, one month after, he was admitted for the second time because paraplegia persisted. Laboratory tests, electromyography and imaging were performed, and ALS was diagnosed. Normally, HIV treated patient with ALS tend to have a better prognosis, however this was not the case.

In this case report, we discuss possible association between ALS and immune reconstitution inflammatory syndrome in HIV patients.

Introduction

Motor neuron disease (MND) encompasses a collection of rare, incurable and devastating neurological diseases, with an incidence of 2–3 in 100,000 people, resulting in the death of 1 in every 500 people affected [1]. The most common disease in MND spectrum is amyotrophic lateral sclerosis (ALS); nevertheless, the variety also includes spinal muscular atrophy (SMA) and spino-bulbar muscular atrophy (SBMA) [2–5].

The hallmark of ALS is the selective death of upper and lower motor neurons, leading to progressive muscular atrophy, weakness and spasticity [2]. Currently, the etiology and pathology has not been completely elucidated [3]. A multifactorial origin has been proposed, in which environmental agents have been implicated, such as the retroviruses Human T cell Lymphoma Virus 1 (HTLV1), and Human Immunodeficiency Virus (HIV), although no causal relationship has been demonstrated [2–5].

Several cases of sporadic MND-like and ALS-like syndromes have been reported in HIV-positive patients, in whom the presentation and progression of the disease differs in certain key aspects [3–5]. The following report describes the case of an ALS-like syndrome in a patient previously diagnosed with stage C3 HIV infection.

CASE REPORT

A 38 years old male from Lima, Peru recently diagnosed with HIV (baseline CD4+: 220 cells/mm3 and viral load: 67,019 copies/ml); initiated combined antiretroviral therapy (cART).

After two months of cART, spastic paraplegia, pain in the lower limbs and difficulty walking motivated patient admission. The brain and spinal MRI and lumbar puncture were normal. Serum RPR titer had 32 dilutions, with negative VDRL and FTA-Abs in the cerebrospinal fluid (CSF). He received 14 days of Penicillin G

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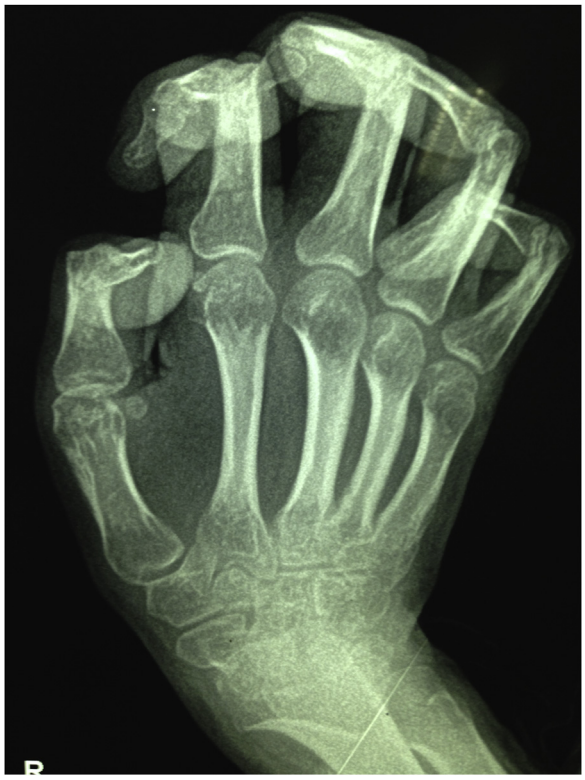

Fig. 1. Fixed flexion deformity in fingers of both hands.

sodium followed by three doses of benzathine penicillin at 2,400,000 IU per week.

One month later, patient was readmitted due to persistence of spastic paraplegia and new onset pain in the right shoulder, with progression to both upper limbs and a fixed flexion deformity in fingers of both hands (Fig. 1). No changes in cognitive status, mild right pharyngeal ptosis with right sided uvula deviation and remaining cranial nerves intact. Additionally, muscle atrophy, weakness and reduced reflexes in the extremities. Bilateral lower limbs paresis, with positive Babinski signs were also present. Sensory exploration was preserved.

Laboratory test were ordered and following the results (Table 1 and 2), differential diagnosis of MND was proposed due the previous history of treatment for neurosyphilis, progressive neurologic decline with decrease in serum RPR titre (4 dilutions) (Table 2) and undetectable HIV viral load. Consequently, electromyography (EMG) (Table 3) and new magnetic resonance imaging (MRI) were performed (Fig. 2). cART was continued with corticosteroids.

Over the course of 1-year, neurological compromise deteriorated, and HIV viral load remained undetectable. Finally, after several years the patient died.

Discussion

ALS in HIV patients is well described; a comparative study between HIV and no HIV patients with MND found that ALS onset was earlier among the HIV group, with regard to non-HIV patients [6]. Also, normally ALS in HIV patients with cART improves in 52 % of cases [7]. It should be noted that clinical response is highly variable [4]. Apparently the non-responsive form may be the ordinary ALS that occurs in HIV infected person [8].

In this case, the cerebrospinal fluid study was normal and there were no images suggestive of structural alterations evidenced in the MRI of the brain and spine. Likewise, the levels of folic acid and vitamin B12 were normal, as well as the thyroid profile. Hence, we propose two possible explanations for the development of ALS-like MND: ALS natural history in HIV, and ALS in the context of Immune reconstitution inflammatory syndrome (IRIS).

IRIS is characterized by a paradoxical worsening of health after cART initiation (few days to 6 months), seen in 13 % of HIV patients [9,10]. It seems to be associated with a previous opportunistic infection; however, it also can present in response to a non-infectious cause [11]. Apparently, there is an important CD8+ lymphocyte infiltration in central and peripheral nerves, as well as a ubiquitous reactive astrocytosis and microglial activation [12,13]. Our patient presented with a worsening 2 months after cART initiation.

In summary, patient developed ALS-like MND after cART initiation probably due to IRIS, being this case report one of the first

Table 1
Auxiliary exams requested in the HNDM.

FBC		LIVER FUNCTION		BIOCHEMISTRY	
Hemoglobin	14.5 g/dl	Total protein	6.92 g/dl	Glucose	102 mg/dl
Hematocrit	40.2 %	Albumin	4.21 g/dl	BUN	17.9 mg/dl
MCV	112 fl	Globulin	2.71 g/dl	Creatinine	0.43 mg/dl
MCH	40.4 pg	Total bilirubin	0.60 mg%	Sodium	141.1 mEq/L
Leucocytes	7,570	Direct bilirubin	0.27 mg%	Potassium	3.85 mEq/L
Neutrophils	5,677	Indirect bilirubin	0.33 mg%	Chloride	111 mEq/L
Band neutrophils	0	AST	33 U/L	Calcium	mg/dl
Lymphocytes	1,286	ALT	43 U/L	Total CPK	180.5 U/L
Eosinophils	151	ALP	83 U/L	CRP	15 mg/L
Monocytes	454	GGT	61 U/L	LDH	434 U/L
Basophils	0	PT	12.7 sec	Uric acid	4.1 mg%
Platelet	254,000	INR	0.89	**URINE TEST**	
Reticulocyte	1.9 %	APTT	39.3 sec	*Leucocytes*	0-1 x/c
		Fibrinogen	326 mg/dl	*Erythrocytes*	0-1 x/c
				Epithelial cells	1-3 x/c

HNDM: Hospital Nacional Dos de Mayo; FBC: full blood count; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; PT: prothrombin time; INR: international normalized ratio; APTT: activated partial thromboplastin time; BUN: blood urea nitrogen; CPK: creatine phosphokinase; CRP: c-reactive protein; LDH: lactate dehydrogenase.

Table 2
Infectious, autoimmune and other non-infectious etiological studies. HNDM.

RPR	4 dilutions	Rheumatoid factor	Negative	LUMBAR PUNCT.	
FTA-Abs	Positive	Anti CCP	Negative	Protein	28 mg/dl
HBsAg	Non-reactive	ANA	Negative	Leucocytes	7 pmmc
Anti HBs	Reactive	c-ANCA	Negative	Lymphocytes	100 %
Anti HBc	Reactive	p-ANCA	Negative	Glucose	65 mg/dl
HBeAg	Non-reactive	Vitamin B12	477.2 pg/ml	*G. index (csf/ser)*	0.6
Anti HBe	Reactive	Folic acid	18.6 ng/ml	Erythrocytes	20 pmmc
IgM anti HAV	Non-reactive	Serum iron	161 ug/dl	ADA	8.6 U/L
Anti HCV	Non-reactive	T.I.B.C	325 ug/dl	FTA-Abs (CSF)	Negative
HTLV 1,2	Non-reactive	Transf. sat%	49.5 %	VDRL (CSF)	Negative
AFB sputum (x3)	Negative	Ferritin	185.9 ng/ml	Bacterial culture	Negative
AFB urine (x3)	Negative	TSH	1.51 uUI/ml	Fungal culture	Negative
AFB stool (x3)	Negative	T4	1.13 ng/ml	MTB culture	Negative
		T3	3.10 pg/ml	Oligoclonal bands	Positive

RPR: rapid plasma reagent; FTA-Abs: fluorescent treponemal antibody absorption; HBsAg: hepatitis B surface antigen; Anti HBs: hepatitis B surface antibody; Anti HBc: hepatitis B core antibody; HBeAg: hepatitis B envelope antigen; IgM anti HAV: immunoglobulin M anti hepatitis A virus; Anti HCV: anti hepatitis C virus; HTLV 1,2: human T lymphotropic virus 1,2; AFB: acid fast bacilli; ANA: antinuclear antibodies; c-ANCA: cytoplasmic antineutrophil cytoplasmic antibodies; p-ANCA: perinuclear antineutrophil cytoplasmic antibodies; Anti CCP: anti citrullinated antibodies; TIBC: total iron binding capacity; Transf. Sat: transferrin saturation; TSH: thyroid stimulating hormone; ADA: adenosine deaminase; MTB: *Mycobacterium tuberculosis*.

Table 3
Neurophysiological studies.

ELECTROMYOGRAPHY (EMG)
Sensitive latency with normal amplitude and conduction velocity in median, cubital, radial and sural nerves.
Prolonged motor latency with low amplitude and conduction velocity in median and cubital nerves. Low amplitude in common peroneal and posterior tibial nerves.
EMG performed with monopolar needle electrodes shows suitable activity during insertion, fibrillation, positive waves and fasciculation in explored muscles, including the tongue, with chronic neurogenic potential, polyphasic waves and incomplete interference pattern in the explored muscles.
EMG CONCLUSION: Compatible with signs of Motor Neuron disease
MAGNETIC RESONANCE IMAGING (MRI)
Brain MRI: no evidence of tumoral, vascular or inflammatory pathologies.
Cervical – dorsal – lumbar sacral MRI: no evidence of tumoral, vascular or inflammatory pathologies.

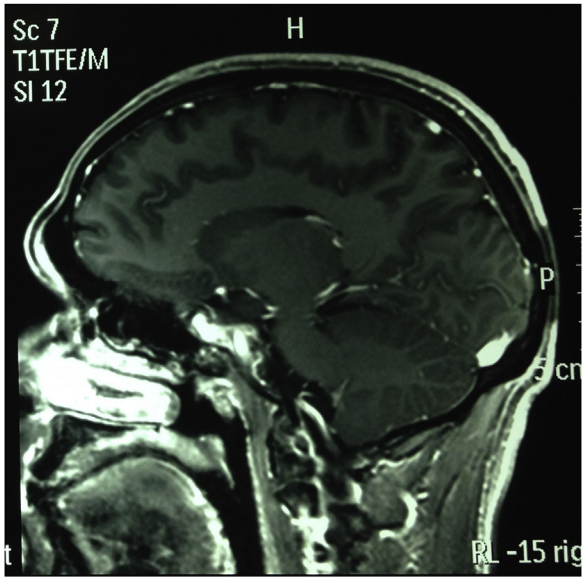

Fig. 2. Latest magnetic resonance imaging (MRI) performed.

to describe this. Further research is needed to elucidate the association between IRIS and ALS.

Author's statement

AQ, JJM, CR, BS, JG, GC, CM, IV and AC have participated in the conception of the article and its writing. IV then collected and summarized the data. AQ, JJM, CR, BS, JG, GC, CM, IV and AC made a critical review of the article. Then, IV made the article corrections gradually. Finally, AC approved the final version.

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Author agreement

I, Andres Quevedo Ramirez, confirm that all authors have agreed the contents of the submission for the paper "Lateral amyotrophic sclerosis-like onset after combined antiretroviral treatment initiation. Case report." on May 30th 2020.

The authors declare having no conflict of interest in the publication of this case report.

Declaration of Competing Interest

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

References

[1] Orrell RW. Motor neuron disease: systematic reviews of treatment for ALS and SMA. Br Med Bull 2010;93:145–59, doi:http://dx.doi.org/10.1093/bmb/ldp049.
[2] Foster LA, Salajegheh MK. Motor neuron disease: pathophysiology, diagnosis, and management. Am J Med 2019;132(1):32–7, doi:http://dx.doi.org/10.1016/j.amjmed.2018.07.012.
[3] Martin S, Al Khleifat A, Al-Chalabi A. What causes amyotrophic lateral sclerosis? F1000Res 2017;6, doi:http://dx.doi.org/10.12688/f1000research.10476.1.

[4] Bowen LN, Tyagi R, Li W, et al. HIV-associated motor neuron disease: HERV-K activation and response to antiretroviral therapy. Neurology 2016;87 (17):1756–62, doi:http://dx.doi.org/10.1212/WNL.0000000000003258.
[5] Lorenzoni PJ, Ducci RD-P, Dalledone GO, et al. Motor neuron disease in patients with HIV infection: report of two cases and brief review of the literature. Clin Neurol Neurosurg 2018;171:139–42, doi:http://dx.doi.org/10.1016/j.clineuro.2018.06.006.
[6] Moodley K, Bill PLA, Bhigjee AI, Patel VB. A comparative stu dy of motor neuron disease in HIV-infected and HIV-uninfected patients. J Neurol Sci 2019;397:96–102, doi:http://dx.doi.org/10.1016/j.jns.2018.12.030.
[7] Alfahad T, Nath A. Retroviruses and amyotrophic lateral sclerosis. Antiviral Res 2013;99(2):180–7, doi:http://dx.doi.org/10.1016/j.antiviral.2013.05.006.
[8] Rowland LP. HIV-related neuromuscular diseases: nemaline myopathy, amyotrophic lateral sclerosis and bibrachial amyotrophic diplegia. Acta Myol 2011;30(1):29–31.
[9] Schütz SG, Robinson-Papp J. HIV-related neuropathy: current perspectives. HIV AIDS (Auckl) 2013;5:243–51, doi:http://dx.doi.org/10.2147/HIV.S36674.
[10] Walker NF, Scriven J, Meintjes G, Wilkinson RJ. Immune reconstitution inflammatory syndrome in HIV-infected patients. HIV AIDS (Auckl) 2015;7:49–64, doi:http://dx.doi.org/10.2147/HIV.S42328.
[11] Kolson D. Neurologic complications of HIV infection in the era of antiretroviral therapy. Top Antivir Med 2017;25(3):97–101.
[12] Post MJD, Thurnher MM, Clifford DB, et al. CNS–immune reconstitution inflammatory syndrome in the setting of HIV infection, part 2: discussion of neuro–immune reconstitution inflammatory syndrome with and without other pathogens. AJNR Am J Neuroradiol 2013;34(7):1308–18, doi:http://dx.doi.org/10.3174/ajnr.A3184.
[13] Johnson TP, Nath A. New insights into immune reconstitution inflammatory syndrome of the central nervous system. Curr Opin HIV AIDS 2014;9(6):572–8, doi:http://dx.doi.org/10.1097/COH.0000000000000107.