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A comparative study of motor neuron disease in HIV-infected and HIV-uninfected patients

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ABSTRACT

Background: This study is a descriptive review of the clinical and treatment outcome differences in HIV-infected patients with motor neuron syndrome (MNS) and HIV-uninfected patients with motor neuron disease (MND).
Methods: A retrospective analysis of patients with MND/S was performed at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa between 2003 and 2017.
Results: One hundred and thirty six patients were included in the study, 101 (76%) were HIV-uninfected and 35 (26%) were HIV-infected. Ninety four percent of the HIV-infected cohort were < 50 years, median 41, IQR (33–45), p < 0.001, had median ALS functional rating scale revised (ALSFRS-R) score of 28, IQR [24–30] and 40% of these patients on anti-retroviral therapy (ART) survived longer than 10 years. Ninety one percent of the HIV-uninfected cohort were > 50 years, median 66, IQR(57–74), *P* < 0.001, had median ALSFRS-R score of 44 (IQR 42–45) and 93% died within 5 years of their illness.
Conclusion: HIV-infected MNS patients were younger, had more severe disease at presentation and survived longer if treated with ART with possible reversal of the disease process, compared to patients with MND.

1. Introduction and background

Several human immunodeficiency virus (HIV) associated neuromuscular syndromes have been described' namely symmetrical polyneuropathies [1], inflammatory demyelinating polyneuropathies [2], inflammatory myopathies [3], neuromuscular junction disorders such as myasthenia gravis [4] and pure motor syndromes such as motor neuron syndrome (MNS) and ventral root radiculopathies (VRR) [5,6].

In HIV-uninfected patients, motor neuron disease (MND) is a progressive neurodegenerative disease with mortality exceeding 90% within 5 years [6]. The clinical presentation of MND is diverse and includes amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), progressive bulbar palsy (PBP) and progressive muscular atrophy (PMA) [7]. Various genetic mutations have been described in sporadic and familial MND which include C9orf72, TARDBK, SOD1, TBK1, NEK1 [8,9]. MND may be an oligogenic disease and in addition to "causative" genes various "other genes" have been reported to modify the phenotype [9,10]. Environmental factors such as insecticides, mechanical trauma, smoking, viruses and epigenetic factors may have a role in the pathogenesis of MND [9,10]. Viruses including the human endogenous retrovirus type-K (HERV-K) and other retroviruses have been implicated in MND [11–17].

MNS is an uncommon neurological complication of HIV-infection limited to a few reported cases [18–21]. Studies have implied that HERV-K may have an important pathogenetic association in both HIV-infected MNS and MND [11–22]. Therefore combined genetic and epidemiological studies are required to better understand the viral or immune basis of HIV-infected MNS. The combination of environmental and epigenetic factors may be pivotal in the development of MND. In this article, we describe and compare the outcomes of 35 HIV-infected patients with MNS and 101 HIV-uninfected patients with MND.

2. Methods

This study is a retrospective chart review, using ICD-10 codes for MND/S from 2003 to 2017. The study was carried out at the Department of Neurology, Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa.

2.1. Standard protocol approvals

Ethical approval was obtained from the Biomedical Research Ethics Committee at the University of KwaZulu-Natal (KZN), ethics number BE272/15. Although not required, as the study was a retrospective chart review, telephonic consent was obtained from patients who were alive.

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Inclusion criteria were patients with pure motor syndromes with known HIV status, who fulfilled clinical and electrophysiological EL Escorial criteria for motor neuron disease, and included those who had a progressive pure LMN presentation not attributable to any other aetiologies and therefore most likely represented PMA [23].

Exclusion criteria were unknown HIV status, pure motor neuropathies attributable to other aetiologies such as multifocal motor neuropathy with conduction blocks, spinal muscular atrophy, infective or inflammatory conditions such as viral infections (HTLV1, HSV, CMV, enteroviruses, and echo viruses), tuberculosis, syphilis, malignancies (myeloma), paraneoplastic radiculopathies, connective tissue diseases and endocrine disorders such as insulinoma and hyperparathyroidism. Patients with HIV-associated VRR were excluded from the study. From our local experience and according to Benatar et al. HIV associated VRR may represent a distinct clinical entity [5]. These patients present with ventral root enhancement on MRI and respond to corticosteroid therapy making MNS/MND less likely [5].

All patients (MND/S) were screened for the above diseases using blood tests (including antiganglioside antibodies, paraneoplastic antibodies, insulin levels, parathyroid hormone), CSF (CMV, HSV, HTLV1, enteroviruses, echoviruses PCR, gene expert for TB, FTA), genetic testing for spinal muscular atrophy where clinically indicated, electrophysiological tests and appropriate radiological investigations. The above blood, CSF, electrophysiological and radiological investigations are standard of care routine investigations done on all patients with suspected MND/S and not done for research purposes only. This is because our neurology unit has a high burden of HIV and CNS tuberculosis. Therefore exclusion of infective and inflammatory disorders as mimics of MND is imperative.

Electrophysiological tests included nerve conduction studies of all four limbs and EMGs of at least three of the following regions that is; lumbar-sacral, thoracic, cervical and bulbar. All HIV-infected patients had contrast administered during MRI spine and brain to exclude infective/inflammatory lesions. HIV-uninfected patients had un-contrasted MRI imaging of the brain and spine. Contrast was administered at the discretion of the radiologist if any suspicious lesion was identified.

Information was extracted from patient records and longitudinal information was obtained by contacting surviving patients or their relatives. Information extracted included demographic features, onset, duration and progression of disease, medical co-morbidities clinical features regarding limb weakness, fasciculations, bulbar symptoms, sensory symptoms, ALSFRS-R scores [24] at diagnosis and 6 monthly intervals up to 18 months (or longer if available), CD4 counts, HIV viral loads, CSF, blood results, MRI and response to therapy, which included antiretroviral therapy (ART) or corticosteroids.

HIV-infected patients with MNS were compared to HIV-uninfected patients with MND for differences in demographic data, onset and progression of disease, CSF findings, electrophysiological and radiological findings and response to therapy (ART or corticosteroids).

The primary aim of the study was to determine if there is a difference in survival outcomes between HIV-infected MNS patients and HIV-uninfected MND patients and to determine the effect of ART on disease progression in the MNS category. This was done by assessing rate of disease progression at six-monthly intervals up to 18 months using the ALSFRS-R scores and correlating these scores with CD4 counts and viral loads. Secondary aims included demographic, clinical, radiological and CSF differences between the two categories.

3. Data availability

Anonymized data will be shared by request from any qualified investigator.

3.1. Statistical analysis

Data was entered in Microsoft Excel and analysed using Prism Software. Descriptive statistics such as percentages, inter-quartile ranges (IQR), medians and *P*-values were used to summarise the results in the HIV-infected and HIV-uninfected categories. A subgroup analysis was also performed among black patients with MND and MNS. Tests used to calculate the above included: Fisher Exact Test for categorical variables, Mann Whitney *U* Test for continuous variables, Spearman Test for correlation between CD4 counts, HIV viral loads and functional scores. A *P*-value of < 0.05 was regarded as being significant.

Indirect standardization was used to compare the study population to the KwaZulu-Natal population, adjusted for differing age distributions and race in the HIV-infected and HIV-uninfected population. The age and race specific MND/S prevalence rates/100000 were estimated from the mid-year population of KwaZulu Natal 2017 [25–27]. A standardized mortality ratio (SMR) was calculated from the sum of expected number of deaths in each stratum using the total KZN population. The Kaplan Meier curve expressed survival in both categories up to 120 months.

4. Results

4.1. Demographic features

One hundred and fifty two patient charts were reviewed. In the HIV-infected category, one patient had HTLV1 infection, two had genetically proven spinal muscular atrophy (SMA) and 11 patients had steroid responsive VRR. In the HIV-uninfected category, one patient had genetically proven spinal muscular atrophy and one patient had multifocal motor neuropathy with conduction blocks with positive anti GM1 antibodies. These 16 patients were excluded from the study (Fig. 1).

One hundred and thirty six patients were diagnosed with MNS/D; 101 (76%) were HIV- uninfected MND and 35 (26%) were HIV-infected MNS. (Table 1). The median age in the HIV un-infected category was 66 (IQR 57–74) and in the HIV-infected category 41 (IQR 33–45). Thirty three (94%) of the HIV-infected patients were < 50 years of age whereas 91 (91%) of the HIV-uninfected patients were over 50 years at the time of presentation. Racial categories in the HIV-infected category included 33 (94%) Black African, 1(3%) White and 1(3%) Indian, whereas in the HIV-uninfected category 39 (39%) were Black African, 21(21%) White and 41(41%) Indian. This equates to MND race adjusted prevalence rates/100000 in KZN of 0.44 among Black Africans, 4.1 among Indians and 4.4 among Whites. The MNS race adjusted prevalence rates/100000 in KZN were 2.4, 10 and 40 for Black Africans, Indians and Whites respectively [25,26]. Age standardization in the MNS category showed highest prevalence rates/100000 between the age groups 40–44 years, 45-49 years which was 2.8 and 3.77 respectively whereas in the MND category the age adjusted prevalence rates/100000 over the age of 65 yrs. ranged from 8 to 12 [25,26,28]. Similar age categories were compared for the Black African sub-analysis only. See Table 3.Comparisons between the other 2 race groups were not done as numbers were too small for any valuable comparison.

4.2. Clinical presentation

All patients in this study had sporadic MND. The median time from onset of motor symptoms to presentation was 15 months in the MND group and five months in the MNS group. In 10 HIV-infected patients, MNS was the presenting illness of HIV. Seventeen (49%) of the HIV-infected category presented with a combination of quadriparesis and bulbar-respiratory symptoms compared to 18 (18%) of the HIV-uninfected category. This correlated with the lower median ALSFRS-R score (median 28) in the HIV-infected category compared to HIV-uninfected category (median 44). Twenty seven patients (78%) in the HIV-infected category presented with ALS, 8(22%) with progressive bulbar palsy,

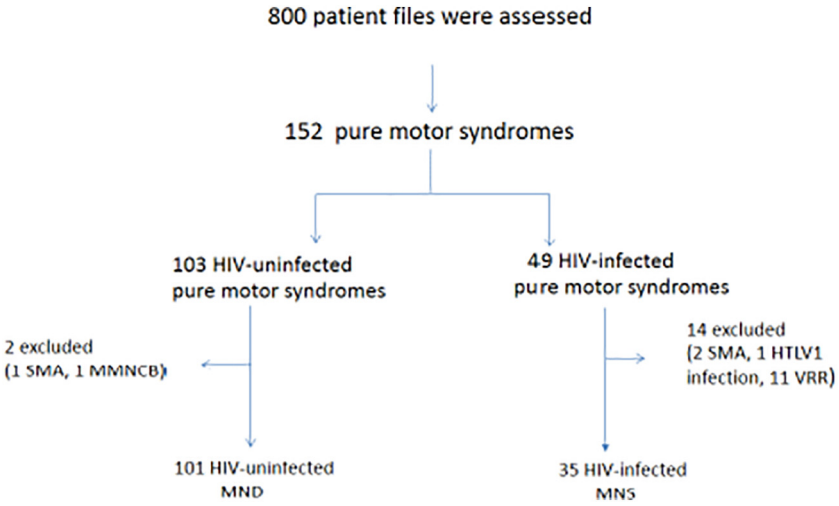

Fig. 1. Consort diagram describing data analysis. HIV = Human Immunodeficiency Virus, SMA = Spinal Muscular atrophy, MMNCB = Multifocal motor neuropathy with conduction blocks, HTLV1 = Human T cell lymphocytic virus type 1, VRR = Ventral Root radiculopathy, MND = Motor Neuron Disease, MNS = Motor Neuron Syndrome.

and 0(0%) with PLS or PMA. In the HIV-uninfected category 52 patients (52%) presented with ALS, 36 (36%) with PBP, 23(23%) with PMA. Nineteen (55%) of HIV-infected MNS had symmetrical signs at onset, and 16(16%) in the MND category.

4.3. Electrophysiology

The electrophysiological findings are summarised in Table 2 (Online supplementary data). All patients had preserved sensory nerve action potentials (SNAPS). Fifteen (15%) of HIV-uninfected patients and eleven (32%) of HIV- infected patients had sural sensory amplitudes 50%–75% below the lower limit of normal, adjusted for age normative values. Seventy five percent (76/101) of HIV-uninfected patients and 100% (35/35) of HIV-infected patients had fasciculations on EMG. Thirty nine (89%) HIV-infected patients had thoracic para-spinal denervation and 29(82%) had tongue fasciculations.

4.4. Radiology

Brain MRI imaging changes included Wallerian degeneration in 48% (48/101) of the HIV-uninfected category and 57% (20/35) of the HIV-infected category. (Fig. 2, image 1, Table 1). None of the MNS patients had root enhancement on MRI spine or signal change on MRI brain or spine to support a vacuolar myelopathy or HIV associated dementia.

4.5. CSF

CSF lymphocyte counts and protein levels were elevated in the HIV-infected category ($P < .001$). CSF was normal in the HIV-uninfected patients (Table 1).

4.6. Survival outcome

The Kaplan-Meier curve (Fig. 3) demonstrates survival in both categories of patients where longitudinal data was available. This included 65% (26/35) in the HIV-infected population and 85% (86/101) in the HIV-uninfected population. Rapid mortality occurred in both groups within 12 months; 35% (8/26) in the HIV-infected category and 20% (12/86) in the HIV-uninfected category. Thereafter HIV-uninfected patients continued to die, with the majority of deaths occurring within 5 years and three patients with progressive muscle atrophy survived beyond 10 years.

In the HIV-infected category, if patients survived beyond 12 months, the likelihood of long-term survival is higher compared to the HIV-uninfected category. Seventeen of the ART treated HIV-infected MND patients survived > 10 years. HIV-uninfected patients are more likely to die of MND than the ART treated HIV-infected patients (96% vs 39%, $P < .001$, OR 37.5, 95% CI: 10.7–131.5). However there is also a shorter time to death in the HIV-infected category especially in the first 12 months when patients are ART naïve or suffer immune reconstitution inflammatory syndrome (median time 8 months; IQR 8–10) compared to the HIV-uninfected category (median time 18 months; IQR 12–26). The standardized mortality ratio was 0.54 (95% CI 0.43–0.65), which implies that mortality is 50% lower in the HIV-infected category compared to the HIV-uninfected category which was statistically significant.

The cause of death in 83% (15/18) of the HIV-infected category was due to MNS, 17% (3/18) were unknown or unrelated. One HIV-infected patient died of an aspiration pneumonia despite immune reconstitution. In the HIV-uninfected category 81% (80/101) of deaths were due to MND and 19% (21/101) were unrelated or unknown.

4.7. Relationship between CD4 count, viral load and functional scores

Fig. 4 shows a relationship between CD4 counts, HIV viral loads and ALSFRS-R scores respectively. This graph suggests that there may be a correlation between immune reconstitution and functional recovery. The above may imply a viral or immunological pathogenesis given the benefit of ART. All HIV-infected patients were initially ART naïve and commenced on ARTs (regimen 1a: Stavudine, lamivudine, efavirenz) after the diagnosis of MNS. This resulted in immune reconstitution (rising CD4 counts and decreasing viral loads), which correlated with clinical recovery reflected by increasing ALSFRS- R score in all except one HIV-infected patient. Five patients (14%) were treated with IVI methylprednisone at a dose of 1 g daily IVI with no clinical response.

4.8. Significant demographic, clinical, electrophysiological and CSF differences between Black African patients with MND and MNS

Table 3 shows a subgroup analysis between Black African patients with MND and MNS. Significant differences are that Black African patients with MNS are younger (median age of 41, IQR 33–44), present earlier (median 5 months, IQR,2–6), have more severe disease and lower ALSFRS-R scores (median of 26,IQR 24–28) compared to Black African patients with MND who are older (median age 63, IQR 54–74), present later (median of 22 months IQR 12–25),and have less severe disease (median ALSFRS-R Score 43, IQR 41–44). MNS patients were more likely to present with symmetrical signs and a combination of quadriparesis and respiratory-bulbar symptoms. A greater number of Black African MNS patients had fasciculations, thoracic paraspinal denervation and tongue fasiculations compared to Black African MND

Table 1
Demographic, clinical, radiological and laboratory findings of HIV-infected MNS and HIV-uninfected MND.

Demographic features	HIV- uninfected $N = 101$	HIV-infected $N = 35$	*P* Value
	N (%)	N (%)	
Age			< 0.001
Median(IQR)	66 (57–74)	41 (33–45)	
< 50 yrs	9 (9)	33 (94)	
50-64 yrs	39 (39)	2 (6)	
65-90 yrs	53 (52)	0 (0)	
Sex			0.3
Males	41 (41)	18 (51)	
Race			< 0.001
Black African	39 (39)/0.44[a]	33 (94)/2.4[a]	
White	21 (21)/4.4[a]	1 (3)/40[a]	
Indian	41 (41)/4.1[a]	1 (3)/10[a]	
Medical comorbidities			
T2 Diabetes Mellitus	22 (22)	0 (0)	< 0.001
Hypertension	15 (15)	2 (6)	< 0.001
Median time from onset of disease to presentation (months)	15 (6–24)	5 (3–9)	< 0.001
Clinical Presentation at diagnosis			
Quadriparesis only	34 (34)	12 (34)	
Paraparesis only	3 (3)	1 (3)	
Upper limb weakness only	16 (16)	2 (6)	
Bulbar only	18 (18)	2 (6)	
Respiratory only	0 (0)	1 (3)	
Monoparesis only	12 (12)	0 (0)	
Combination of the above	18 (18)	17 (49)	
Symmetry at onset	16 (16)	19 (55)	< 0.001
MND subtype			
ALS	52 (52)	27 (78)	< 0.001
PLS	0 (0)	0 (0)	
PBP	36 (36)	8 (22)	
PMA	23 (23)	0 (0)	
ALSFRS-R Scores at presentation			
Median (IQR)	44(42–45)	28(24–30)	
Time to death (months)			
Median,(IQR)	18 (12–26)	8 (8–10)	
Alive (at 10 years)	3 (3)	17 (48)	< 0.001
Cause of death			
Related to MND	80 (81)	15 (83)	
Unrelated or unknown	21 (19)	3 (17)	
ARV naive	101	35	
Radiology			
MRI brain with Wallerian degeneration	48 (48)	20 (57)	
CSF Results			
Protein (g/dl)	0.39 (0.32–0.45)	0.68 (0.41–0.92)	< 0.001
Glucose(mmol/L)	4.1 (3.6–4.5)	3.9 (3.4–4.2)	
Lymphocyte count (cells/ul)	0 (0–0)	6 (2 – 12)	< 0.001
Polymorphocyte count(cells/ul)	0 (0–0)	0 (0–0)	

ALS = Amyotrophic Lateral Sclerosis, PLS = Primary Lateral Sclerosis, PBP = Progressive Bulbar Palsy, PMA = Primary Muscular Atrophy.

[a] Prevalence rates /100000 in KZN adjusted according to race and HIV status.

patients. The CSF also showed higher lymphocyte and protein counts compared to the black MND subcategory. Sixteen Black African MNS patients survived with ART and those who did die, died earlier in the disease if untreated. Even after indirect age standardization between HIV-infected and HIV-uninfected Black African patients in KZN, MNS was still more prevalent among younger patients in the MNS category (1.66/100000 in age category < 50 yrs) compared to the Black African MND subgroup where prevalence/100000 was 3.9 in age category 65-90 yrs. See comparisons for similar age categories in Table 3.

5. Discussion

Despite HIV-infected MNS being regarded as a potentially reversible motor neuron syndrome of viral or immune mediated origin, both MND and MNS meet the clinical and electrophysiological revised EL-Escorial criteria for MND and were therefore compared in this study. Both MND and MNS may both potentially have similar reversible aetiopathogeneses, with a possible response to ARTs in both categories although no studies using ART in the HIV-uninfected category has been published to date. Important differences in the MNS group include the following: majority were young Black African, greater severity of disease at presentation, recovery with ART, and reactive CSF.

Younger age and racial predilection may represent an artefact of the study population as most HIV-infected patients in South Africa are young Black African [25–27]. Ninety four percent (33/39) of the HIV-infected MNS and 39% (39/101), of the HIV-uninfected MND patients were Black African, which equates to prevalence rates among HIV-infected and HIV-uninfected Black Africans in KZN of 2.4/100000 and 0.44/100000 respectively [25,26]. Cosnett et al. reported a prevalence rate of 0.88/100000 among Black African patients with MND (HIV status unknown) in 1989 in KZN [29]. The peak age of presentation was the 4th decade compared to Indian and European patients who presented two decades later. According to Cosnett, the earlier presentation among Black African patients, which is consistent with the MNS cohort, may suggest a genomic difference between the race groups, environmental factor exposure or reflect a referral bias when standardized for age and race. Cosnett et al., reported high rates of poliovirus and HTLV1 and mechanical trauma among Black African patients which maybe a contributing factor.

In the subgroup analysis of black patients only, MNS occurs in younger black patients, presents earlier and with more aggressive disease (both clinically and electrophysiologically, Table 3) compared to black MND patients, thereby eliminating race as a confounder. This therefore suggests that HIV infection maybe a key factor in the aetiopathogenesis of MNS and not genomic differences between race groups.

Conclusions regarding racial differences in the other race groups would be unreliable given the small number of Indian and European patients who were HIV-infected. However after age standardization and adjustment for race the study shows that MND is still more prevalent in elderly Europeans ranging from 8 to 12/100000 compared to prevalence rates of 3.9/100000 among black MND patients between age groups 65–90 years. In the MNS category when adjusted for age, the disease is still more prevalent in the 3rd and 4th decade and equates to prevalence rates of 1.66/100000 in black patients < 50 years of age.

Comparisons with other studies from Sub-Saharan Africa was not

Table 2
NCS and EMG findings in HIV-infected MNS and HIV-uninfected (For supplementary file, online publication).

	HIV-uninfected n = 101(%)	HIV-infected N = 35(%)	P value
Normal SNAPS in all 4 limbs	86 (85)	24 (68)	
Reduced SNAPs in LL (50%–75% expected value)	15 (15)	11 (32)	
Reduced CMAP (< 50% expected value)	90 (89)	35 (100)	
Fasiculations	76 (75)	35 (100)	
Thoracic paraspinal denervation	64 (63)	31 (89)	< 0.05
Tongue Fasiculations	51 (50)	29 (82)	< 0.001

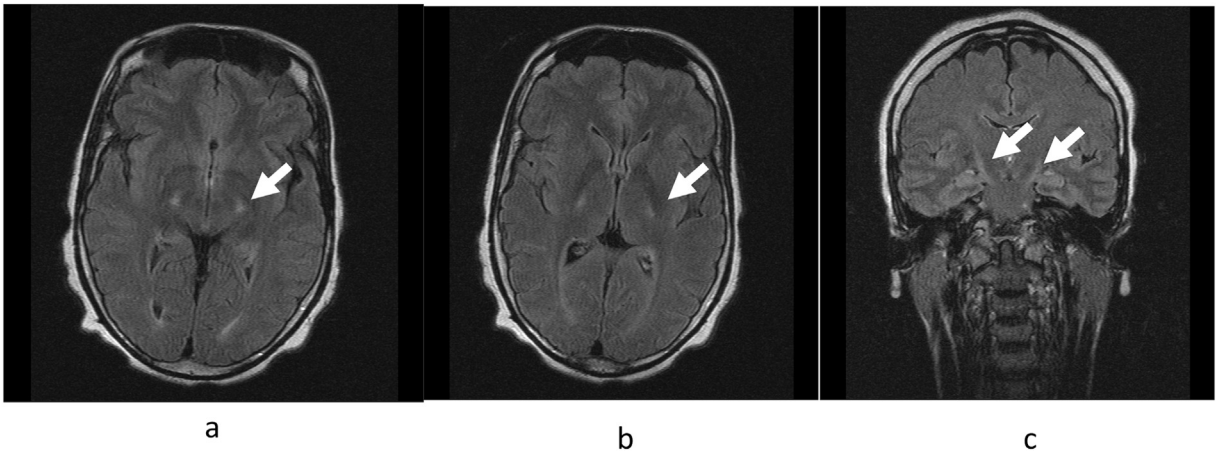

Fig. 2. Radiological features of HIV-infected patients MND (image 1) (Supplementary online publication) Image 1: MRI (T2 Flair) of Wallerian degeneration (arrows) in HIV-infected patient with MND.

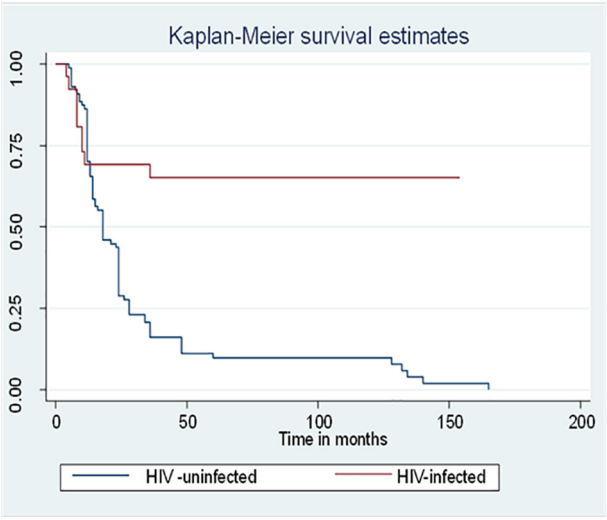

Fig. 3. Kaplan –Meier survival estimates in the HIV-infected and HIV-uninfected categories over time.

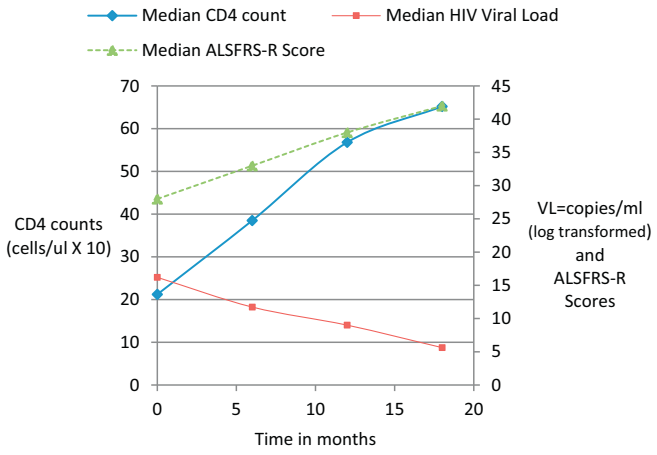

Fig. 4. Relationship between HIV viral Loads, CD4 counts and ALS FRS-R Scores over time.

possible as the results are highly variable and reliability regarding the diagnosis is questionable [30]. However the general consensus was that African patients with MND present earlier than Europeans and progress more rapidly which may be explained by concomitant viral infections or genetic factors [30]. The age adjusted prevalence rates/100000 for MND and MNS in KZN was 3 and 1.64 respectively which is compatible with rates in prospective studies in other parts of the world [25,26,31]. Note that this differs from the age-adjusted results as this prevalence refers to the entire cohort as opposed to the five-year age segments. The

Table 3
Significant ($P < 0.001$) demographic, clinical, electrophysiological and CSF differences between Black African patients with MND and MNS.

	HIV-infected MNS ($N = 33$)	HIV-uninfected MND ($N = 39$)
	N (%)	N (%)
Age		
Median (IQR)	41 (33–44)	63 (54–74)
< 50 yrs	31 (84%)[a]1.66	6 (15%)[a] 0.36
50–64 yrs	2 (12%)[a]0.89	15 (38%)[a]1.94
65–90 yrs	0 (0%)[a] 0	18 (46%)[a]3.9
Sex		
Male	18 (31)	21 (54)
Median time from onset of disease to presentation (months)		
Months (IQR)	5 (2–6)	22 (12–25)
Clinical presentation at diagnosis		
Quadriparesis + respiratory bulbar symptoms	16 (67)	8 (33)
ALS scores at presentation		
Median (IQR)	26 (24–28)	43 (41–44)
Symmetry at onset	11 (33)	4 (10)
Medical comorbidities		
T2 diabetes mellitus	1 (3)	7 (18%)
Hypertension	1 (3)	5 (13%)
Electrophysiology		
Fasiculations	33 (100)	23 (58)
Thoracic paraspinal denervation	30 (91)	20 (51)
Tongue fasiculations	27 (81)	10 (25)
CSF		
Lymphocytes (cells/ul)	8 (4–12)	0 (0–0)
Polymorphs (cells/ul)	0 (0–2)	0 (0–0)
Protein (g/dl)	0.78 (0.4–0.9)	0.38 (0.3–0.4)
Glucose (mmol/L)	3.9 (3.4–4.2)	4.1 (3.7–4.8)
Time to death (months)		
Median (IQR)	8 (6–11)	20 (22–28)
Alive at 10 yrs	16 (49)	0 (0)
Cause of death		
Related to MND/S	15 (45)	28 (71)
Unrelated or unknown	2 (6)	11 (28)

Other categories with PV > 0.05 not in the table include: Gender, Subtypes of MND and Radiology.

[a] Prevalence rates/100000 in KZN adjusted according to race and HIV status.

race adjusted prevalence rates for the Black African patients with MND in KZN was lower (0.44/100000) which is also consistent with the belief that MND is uncommon among Black African Africans [31]. However when adjusting for age the prevalence rates of MND among black Africans increases to 3.9/100000 in the age category 65-90 yrs. The higher prevalence rates of 1.66/100000 among Black Africans in the MNS group in age < 50 yrs. compared to 0.36/100000 in the same age category in the black African MND group, supports the hypothesis that HIV-infection is a confounder (Table 3).

Greater disease severity at presentation is suggested by lower ALSFRS-R score, greater symmetry of signs at presentation, and greater denervation on EMG, which included the thoracic paraspinal and the tongue muscles. This "advanced stage of ALS" is consistent with the findings reported by Cosnett et al. among Black African patients who presented with advanced ALS rather than the benign variety. Many patients in this cohort may have had co-existent HIV-infection or HERV-K infection. Immunodeficiency, genetic factors and possibly higher CSF HERV-K viral loads may contribute to faster progression of disease in the MNS category. One may also postulate that HIV promotes the expression of HERV-K. There have been no studies to correlate CSF HERV-K viral loads with clinical manifestation.

Functional recovery corresponded with immune reconstitution after ART therapy in the MNS category of patients. If patients survived > 12 months after ART, they had reversal of disease with time. Seventeen patients survived longer than 10 years after ART in the MNS category. Reasons for longer survival comparing those that demised versus those that survived in the MNS category include early presentation, less disability at presentation, early commencement of ART and quick immune reconstitution. A multivariate analysis between the two categories was not attempted as the numbers were too small to draw reliable conclusions.

The inflammatory CSF changes are compatible with changes that occur with HIV [32]. As in previous studies, the HIV population had a significant lymphocytosis and raised CSF protein levels compared with the HIV-uninfected MND group. This is probably due to HIV CSF viral replication or may represent replication of other retroviruses not routinely tested for example HERV-K. More studies are therefore required to study CSF changes in HIV-infected MNS patients compared with HIV-infected patients without MNS.

Although HIV-infected MNS and MND are thought to be separate disease entities, MNS being infective or inflammatory and MND neurodegenerative, both categories of patients have similar clinical presentation and there is supporting evidence for a retrovirus contribution to disease in both categories [16,17,22,33,34]. Therefore the MNS category of patients is an important model to investigate the retroviral postulate in MND. Supporting literature by Westarp et al. suggests that HIV-uninfected patients with sporadic MND had high circulating immune complexes and antibodies against the human spuma retrovirus compared to controls. These levels decreased after ART supporting the contention that sporadic MND maybe retrovirus induced [17,22]. Previous studies have identified reverse transcriptase in patients with HIV-uninfected MND at levels comparable to HIV-infected patients further supporting the above contention [12–14] Post-mortem brain tissue from a number of patients with ALS had significantly higher expression of HERV-K compared to controls [34]. Li W et al. also suggested that HERV- K is activated in a subpopulation of patients with sporadic MND and that its envelope protein may contribute to neurodegeneration [16]. The HERV-K virus was present in cortical and spinal neurons of MND patients but not healthy controls [16,33]. Douville et al. reported high levels of HERV-K *pol* transcripts with a specific pattern of expression including intact open reading frames which where highest in the cortical motor neurons and not detected in Parkinson's disease or accidental-death controls. The HERV-K expression strongly correlated with TDP-43, a multifunctional protein known to be dysregulated in MND [11,35]. Transgenic mice expressing the envelope protein developed progressive motor dysfunction accompanied by selective loss of volume in the motor cortex [16,33].

Bowen et al. described five HIV positive patients with MNS [20]. Three of these had detectable levels of plasma HERV-K, which became undetectable with ART therapy and corresponded to clinical recovery. The remaining two patients showed slow progression of disease. Alternatively, one may consider an immune pathogenesis for MNS as a result of T-regulatory cell reduction, while ART results in restoration of T-regulatory cells inducing immune tolerance and promoting recovery [36]. More recently HERV-K protein has become important targets for autoimmune disease and malignancy due to complex interactions between HERV-K and the immune system [37]. Larger prospective studies are required to better understand the role of HERV-K in MND.

The above viral hypothesis is consistent with the "multistep hypothesis" of MND which states that genetic mutations alone cannot fully explain MND and that various environmental factors are likely to trigger molecular steps [9,10]. The identification of reduced number of steps in patients with genetic mutations compared to those without mutations strongly supports the idea that MND is a multistep process and the viral aetiology may provide a clue for uncovering the pathogenesis of MND [10]. The value of ART in HIV-uninfected MND is uncertain. However, a pilot trial of ART in early HIV-uninfected MND may prove illuminating.

Limitations of the study include comparison of two disease entities with similar clinical manifestation but possibly different aetiopathogenesis. However, the possibility that MND may have a viral contribution still exists. Other limitations include retrospective design, referral and race bias, erroneous coding and the exact aetiology of death may have not been obtained at follow up in some patients.

6. Conclusion

This study suggests that HIV-infected patients with MNS are more functionally disabled at presentation and die within the first year if untreated. ART therapy results in improved functional recovery with possible reversal of the disease process, which supports a viral or immune pathogenesis. Future prospective studies are required to evaluate the pathogenesis of HIV-associated MNS. This may extend clues to the "multi-step" pathogenesis of MND. Lastly active support for patients with MNS in the long term is warranted as survival and improvement is possible.

Author contributions

Kaminie Moodley: developed concept, collected and analysed data, generated manuscript.

Vinod B Patel developed concepts and helped with planning analysis and review of the manuscript. PLA Bill: review of manuscript. AI Bhigjee: Review of manuscript.

Statistical analysis conducted by Cathy Connolly (PHD), University of KwaZulu-Natal.

Author disclosures

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References

[1] J. Maritz, M. Benatar, J.A. Dave, et al., HIV neuropathy in South Africans: frequency, characteristics, and risk factors, Muscle Nerve 41 (2010) 599–606.
[2] K. Moodley, P.L. Bill, V.B. Patel, A comparative study of CIDP in a cohort of HIV-infected and HIV-uninfected patients, Neurol. Neuroimmunol. Neuroinflamm. 4 (2017) e315.
[3] M.R. Freitas, M.A. Neves, O.J. Nascimento, M.P. de Mello, J.P. Botelho, L. Chimelli, Inclusion body myositis and HIV infection, Arq. Neuropsiquiatr. 66 (2008) 428–430.
[4] S.P. Gorthi, S. Shankar, S. Johri, A. Mishra, N.R. Chaudhary, HIV infection with myasthenia gravis, J. Assoc. Physicians India 53 (2005) 995–996.

[5] M.G. Benatar, R.W. Eastman, Human immunodeficiency virus-associated pure motor lumbosacral polyradiculopathy, Arch. Neurol. 57 (2000) 1034–1039.
[6] D.J. Donohoe, B. Brady, Motor neuron disease: etiology, pathogenesis and treatment—a review, Ir. J. Med. Sci. 165 (1996) 200–209.
[7] M. Swash, Motor neuron disease, Postgrad. Med. J. 68 (1992) 533–537.
[8] P.A. Dion, H. Daoud, G.A. Rouleau, Genetics of motor neuron disorders: new insights into pathogenic mechanisms, Nat. Rev. Genet. 10 (2009) 769–782.
[9] A. Al-Chalabi, O. Hardiman, The epidemiology of ALS: a conspiracy of genes, environment and time, Nat. Rev. Neurol. 9 (2013) 617–628.
[10] A. Chio, L. Mazzini, S. D'Alfonso, et al., The multistep hypothesis of ALS revisited: the role of genetic mutations, Neurology 91 (2018) e635–e642.
[11] R. Douville, J. Liu, J. Rothstein, A. Nath, Identification of active loci of a human endogenous retrovirus in neurons of patients with amyotrophic lateral sclerosis, Ann. Neurol. 69 (2011) 141–151.
[12] A.J. Steele, A. Al-Chalabi, K. Ferrante, M.E. Cudkowicz, R.H. Brown Jr., J.A. Garson, Detection of serum reverse transcriptase activity in patients with ALS and unaffected blood relatives, Neurology 64 (2005) 454–458.
[13] D.J. MacGowan, S.N. Scelsa, T.E. Imperato, K.N. Liu, P. Baron, B. Polsky, A controlled study of reverse transcriptase in serum and CSF of HIV-negative patients with ALS, Neurology 68 (2007) 1944–1946.
[14] McCormick AL, Brown RH, Jr., Cudkowicz ME, Al-Chalabi A, Garson JA. Quantification of reverse transcriptase in ALS and elimination of a novel retroviral candidate. Neurology 2008;70:278–283.
[15] M.E. Westarp, P. Ferrante, H. Perron, P. Bartmann, H.H. Kornhuber, Sporadic ALS/MND: a global neurodegeneration with retroviral involvement? J. Neurol. Sci. 129 (Suppl) (1995) 145–147.
[16] W. Li, M.H. Lee, L. Henderson, et al., Human endogenous retrovirus-K contributes to motor neuron disease, Sci. Transl. Med. 7 (2015) 307ra153.
[17] M.E. Westarp, D. Fuchs, P. Bartmann, et al., Amyotrophic lateral sclerosis an enigmatic disease with B-cellular and anti-retroviral immune responses, Eur. J. Med. 2 (1993) 327–332.
[18] A. Verma, J.R. Berger, ALS syndrome in patients with HIV-1 infection, J. Neurol. Sci. 240 (2006) 59–64.
[19] A. Moulignier, A. Moulonguet, G. Pialoux, W. Rozenbaum, Reversible ALS-like disorder in HIV infection, Neurology 57 (2001) 995–1001.
[20] L.N. Bowen, R. Tyagi, W. Li, et al., HIV-associated motor neuron disease: HERV-K activation and response to antiretroviral therapy, Neurology 87 (2016) 1756–1762.
[21] H.J. von Giesen, R. Kaiser, H. Koller, K. Wetzel, G. Arendt, Reversible ALS-like disorder in HIV infection. An ALS-like syndrome with new HIV infection and complete response to antiretroviral therapy, Neurology 59 (2002) 474 (author reply 474-475).
[22] M.E. Westarp, P. Bartmann, J. Rossler, et al., Antiretroviral therapy in sporadic adult amyotrophic lateral sclerosis, Neuroreport 4 (1993) 819–822.
[23] A. Ludolph, V. Drory, O. Hardiman, et al., A revision of the El Escorial criteria - 2015, Amyotroph. Lateral Scler. Frontotemporal. Degener. 16 (2015) 291–292.
[24] J. Rooney, T. Burke, A. Vajda, M. Heverin, O. Hardiman, What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis, J. Neurol. Neurosurg. Psychiatry 88 (2017) 381–385.
[25] C. Kenyon, J. Buyze, R. Colebunders, HIV prevalence by race co-varies closely with concurrency and number of sex partners in South Africa, PLoS One 8 (2013) e64080.
[26] A.B.M. Kharsany, C. Cawood, D. Khanyile, et al., Community-based HIV prevalence in KwaZulu-Natal, South Africa: results of a cross-sectional household survey, Lancet HIV 5 (2018) e427–e437.
[27] Mid Term HIV Population Statistics SA [online]. Available at: http://www.statssa.gov.za/publications/P0302/P03022017.pdf. Accessed 13 November.
[28] C. Wallrauch, T. Barnighausen, M.L. Newell, HIV prevalence and incidence in people 50 years and older in rural South Africa, S. Afr. Med. J. 100 (2010) 812–814.
[29] J.E. Cosnett, P.L. Bill, A.I. Bhigjee, Motor neuron disease in blacks. Epidemiological observations in Natal, S. Afr. Med. J. 76 (1989) 155–157.
[30] E. Quansah, T.K. Karikari, Motor neuron diseases in Sub-Saharan Africa: the need for more population-based studies, Biomed. Res. Int. 2015 (2015) 298409.
[31] A. Chio, G. Logroscino, B.J. Traynor, et al., Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature, Neuroepidemiology 41 (2013) 118–130.
[32] J. Peterson, M. Gisslen, H. Zetterberg, et al., Cerebrospinal fluid (CSF) neuronal biomarkers across the spectrum of HIV infection: hierarchy of injury and detection, PLoS One 9 (2014) e116081.
[33] M.E. Westarp, K.P. Westphal, J. Clausen, et al., Retroviral interference with neuronotrophic signaling in human motor neuron disease? Clin. Physiol. Biochem. 10 (1993) 1–7.
[34] T. Alfahad, A. Nath, Retroviruses and amyotrophic lateral sclerosis, Antivir. Res. 99 (2013) 180–187.
[35] R.N. Douville, A. Nath, Human endogenous retrovirus-K and TDP-43 expression bridges ALS and HIV neuropathology, Front. Microbiol. 8 (2017) 1986.
[36] M.F. Chevalier, L. Weiss, The split personality of regulatory T cells in HIV infection, Blood 121 (2013) 29–37.
[37] V. Groger, H. Cynis, Human endogenous retroviruses and their putative role in the development of autoimmune disorders such as multiple sclerosis, Front. Microbiol. 9 (2018) 265.