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MRI findings and use in confused HIV infected patients

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MRI FINDINGS AND USE IN CONFUSED HIV INFECTED PATIENTS

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Diagnostic Radiology

Johannesburg, 2019

Declaration

I, Nikelo Mabandla, declare that this research report is my own work. It is being submitted for the degree of MMed (Rad D) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

DR NIKELO MABANDLA

On this 20th day of May 2019

Dedication

To Mafate and my young kids Bubukho and Nkitha – I am because of you!

My mom, dad, siblings, niece and nephew – you are my strength.

Abstract

INTRODUCTION: HIV/AIDS related neurological disease is important and up to 50% of infected patients present with confusion in their lifetime. CT-based neuroimaging remains key in the management of disease, however access to and use of MRI is increasing. In resource-constrained countries like ours, literature on the use of MRI and the spectrum of MRI-based neurological disease in confused HIV infected patients with focal neurology and a normal prior CT remains scanty.

AIM: The aim of the research was to determine the common MRI brain findings in HIV positive adult patients presenting with confusion, who previously had a CT brain scan.

METHOD: MRI and CT brain scans of confused HIV infected patients from Helen Joseph Hospital, Johannesburg were retrospectively reviewed. The clinical neurological status was documented and analysed in relation to the CT and MRI findings.

RESULTS: Clinical confusion was documented in 26% (87/341) of MRI patients. Focal neurology was present in 87% (67/77) of the 77 included patients. Abnormal MRI findings were detected in 79% (53/67) of the focal neurology cohort. 39% (9/23) of normal CT scans had abnormal subsequent MRI's -13% (3/23) had HAND and 9% (2/23) had CVA. The presence of focal neurology was a strong predictor of abnormal MRI (*p*-value: 0,001).

CONCLUSIONS:

In HIV-infected patients with confusion a significant portion (39%) of MRI scans performed after a prior normal CT was abnormal and underlying HAND or CVA was detected. Furthermore, in the presence of focal neurology and a normal CT scan, an MRI brain is indicated.

Acknowledgements

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Nomenclature

MRI	Magnetic Resonance Imaging
MDCT (CT)	Multi Detector Computed Tomography
CSF	Cerebrospinal Fluid
MMSE	Mini Mental State Examination
GCS	Glasgow Coma Scale
HAND	HIV Associated Neurocognitive Disease
CVA	Cerebrovascular Disease
HSV	Herpes Simplex Virus
PML	Progressive Multifocal Leukoencephalopathy
NHLS	National Health Laboratory Service
ELISA	Enzyme Linked Immunosorbent Assay
SOL's	Space Occupying Lesions
NML	Non-Mass Lesions

1. Introduction

In 2016, 37 million people were living with HIV/AIDS worldwide[1,2], with 71% of these individuals residing in Sub-Saharan Africa[1–3]. Currently approximately 12,7% (7 million) of South Africans are HIV positive, with 19% of the economically active (15-49 year- old) population infected[4].

Up to 50% of AIDS patients present with confusion during their lifetime due to HIV related neurological disease[10]. In these patients, the involvement of the central nervous system (CNS) indicates stage 3 or 4 disease[5] and is a leading cause of mortality[6–9]. Radiological imaging, together with haematological and cerebrospinal fluid (CSF) analysis is crucial in the diagnosis, treatment and surveillance of HIV-associated neurological disease[11].

Whereas magnetic resonance imaging (MRI) is the neuroimaging technique of choice[11], computed tomography (CT) is more easily accessible and therefore, more utilised in Sub-Saharan and developing countries like South Africa[12,13]. Consequently, most local literature and HIV/AIDS related neuroimaging studies are CT-based[8,12,14], with very limited literature on MRI findings in this population. The utilisation of MRI is however growing and locally generated research in this area is essential[13,14].

1.1. Motivation and Rationale

Initial research by Rosenblum (1985) established neurologic disease in up to 70% of HIV-positive patients[15]. Later studies by Weisberg et al (2001) confirmed more than half of HIV-positive patients suffer from neuro-AIDS during their lifetime, and up to 10% of patients with undiagnosed HIV/AIDS initially present with CNS disease[6]. Post mortem analyses also revealed neurological disease in up to 90% of these patients[6,9,15].

Focal neurological deficit consists of a set of symptoms and signs caused by an altered physiological function in one or more focal areas of the central nervous system[16], and may either be acute, particularly in vascular disease, or progressive[16,17]. The chronology of neuro-AIDS symptoms varies depending on factors such as the type of disease and treatment[11,16].

Confusion is an important component in the presentation of neurological disease but is not regarded as a focal neurological deficit[11,16,18]. In the clinical context it is best understood as delirium or altered sensorium. According to Johnson (2001) it can be described as "an aetiologically non-specific organic cerebral syndrome, characterised by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion and the sleep-wake cycle"[18]. Identification and treatment of the precipitating disease or physiological abnormality usually reverses delirium[16,18].

HIV-associated diseases can precipitate delirium, even in the absence of underlying HIV-related neurocognitive disorder (HAND)[18]. Similarly, untreated and prolonged delirium can evolve into a dementia[19]. Thus, in HIV/AIDS, dementia and delirium can occur separately or coexist and may be difficult to distinguish without reliable collateral history[18].

The objective assessments that are utilised in most medical centres include the Confusion Assessment Measurement (CAM)[18], the Mini-Mental State Examination (MMSE)[18] and the Glasgow Comma Scale (GCS)[20] (Appendix A) .

The GCS is the most routinely utilised assessment tool especially in the Emergency Department, and is critical in requesting neuroimaging[11,17,20]. Although its reliability is limited to the assessment of the level of consciousness or coma status of the patient, it is highly sensitive in assessing the neurological status of the patient and establishing possible underlying neurological disease[20,21].

Prior to ARV availability in South Africa, neuro-AIDS as an initial clinical presentation occurred in 7-20% of undiagnosed patients[8]. These statistics remain unchanged and significant prevalence is demonstrated even in patients on ARVs, both locally[8] and in developing countries like India[9].

Whilst the spectrum of disease in neuro-AIDS is well understood, the variety and prevalent neurological disease in the post-ARV era locally remains unclear. Additionally, most studies are CT-based and the utilisation of MRI in the neuro-imaging of these patients remain poorly defined.

This study aimed to determine the prevalent MRI based neurological disease in confused HIV / AIDS patients with prior CT brain scans. It also sought to establish the common diseases (and usefulness of additional MRI scanning) in the context of normal CT imaging. Lastly, we attempted to correlate focal neurological signs to subsequent MRI findings.

1.2. Literature Review

The severity of immunosuppression is the most important aspect of HIV-related CNS disease (neuro-AIDS)[22]. In patients with CD4 counts above 500/mL, the spectrum of disease is similar to the rest of the uninfected population[6,8,22]. HIV encephalopathy and opportunistic infections are common in patients with CD4 200 to 500/mL[22,23], whereas the majority of stage 4 defining disease such as primary CNS lymphoma and other opportunistic infections (OIs) are common in patients with CD4 counts less than 200/mL[5,22,24].

The manifestation of neuro-AIDS can be classified into three main categories[5,6,22–24] namely:

1. Opportunistic Infections (OIs)
2. HIV related neurological disease.
3. HIV/AIDS related neoplastic disease

1.2.1. Opportunistic Infections in HIV-infected Patients

Bacterial, viral and fungal infections result in a spectrum of neurological diseases such as meningitis, encephalitis and focal space occupying lesions such as abscesses and granulomas[22,23,25]. Disseminated tuberculosis (TB), a stage 4 AIDS defining illness, commonly manifests intracranially as meningitis complicated by hydrocephalus[8,17,26].

As demonstrated by Schutte et al (2013), almost 60% (101/173) of HIV-related deaths at Steve Biko Academic Hospital, Pretoria, between 2006 and 2012 were attributed to meningitis[8]. Of these, TB and cryptococcal meningitis accounted for 50% (50/101) and 30% (30/101) of the deaths respectively.

Radiological Findings of Opportunistic Infections

On CT and MRI brain TB presents as a nodular predominantly basal meningitis, with or without focal brain tubercles[17,22,23,26]. There may be concomitant abscesses with associated vasogenic oedema, similar to pyogenic bacterial infections and toxoplasmosis[23].

Communicating hydrocephalus is a common complication of TB meningitis and distinguishes it from toxoplasmosis and granular neurocysticercosis[22,23]. Neuroimaging findings are often normal in uncomplicated meningitis, and CSF analysis is generally necessary to confirm diagnosis[8,22].

Cryptococcus neoformans typically causes a sub-acute to chronic meningitis with non-specific radiological features but can cause typically non-enhancing parenchymal cryptococcomas and gelatinous cysts in the subependymal and in the Virchow-Robison spaces[23,26]. There is usually no associated mass effect or vasogenic oedema, distinguishing it from TB[23,26]. Hydrocephalus and nodular meningeal enhancement similar to TB have also been reported[23,26].

The most common infective space occupying lesions in neuro-AIDS are toxoplasmosis[7] and tuberculomas[17,22,23]. Severe bacterial infections such as Staphylococcus aureus, Streptococcus pneumoniae, etc. may occasionally manifest with pyogenic abscesses. Cryptococcus neoformans and neurocysticercosis also commonly present with cystic space occupying lesions[23,27].

Immunity to the obligate intracellular infection with T. gondii is common in most adults[23,26]. In 10-45% of patients[7,25] latent infection is reactivated leading to toxoplasmosis. Radiologically it manifests as a cerebritis, solid or ring enhancing focal lesions[28] with a predilection for the basal ganglia, typically in patients with a CD4 of less than 100/mL[17]. These may be single or multiple with adjacent vasogenic oedema. TB and fungal infections can closely mimic these findings even on MRI[13,25,26].

Cytomegalovirus (CMV), herpes simplex virus (HSV) and even HIV itself typically cause a nodular ventriculo-encephalitis[22,23]. On neuroimaging this presents as a nodular mass-like enlargement of the temporal lobes, basal ganglia and the brainstem[22,23]. An enhancing ventriculo-encephalitis and progressive ventriculomegaly is also common[22]. HSV and HIV are also common causes of cerebro- encephalitis[23,26].

Table 1.1: Radiological Findings in HIV- associated Opportunistic Infections[17,22,23,25,26]

	Mycobacterium TB	**Bacterial Infection**	**Cryptococcus Neoformans**	**Toxoplasmosis Gondii**	**Viral Infection** (Cytomegalovirus / Herpes Simplex / HIV)
Meningitis	Basal leptomeningeal or nodular	Leptomeningeal surrounds entire brain	Nodular or Leptomeningeal	Not typical	Leptomeningeal or Nodular
Space Occupying Lesions	Random ring enhancing granulomas & vasogenic oedema	Abscess/es	Cryptococcomas and Gelatinous Cysts in perivascular spaces	Abscess/es or Granulomas mainly in basal ganglia & vasogenic oedema	Not typical
Cerebritis	Not typical	Not typical	Not typical	Common	Common in temporal and frontal lobes
Hydrocephalus	Common	Not typical	Uncommon	Not typical	Ventriculitis and ventriculomegaly common

1.2.2. HIV related neurological disease (HAND).

In patients presenting with dementia, motor impairment and neurocognitive dysfunction with no specific neurological disease on imaging and CSF analysis, the clinical diagnosis of HIV associated neurocognitive disease (HAND) is made[17,22,26].

Prevalence varies greatly between countries and is estimated in up to 50% of patients in the developed world[10,26] and less than 5% in countries like Ethiopia[7], Kenya[10] and South Africa[29]. Locally, the current prevalence is down from 16% in the pre-ARV era[29].

The pathogenesis is unclear, but the basal ganglia and brain stem are most commonly affected and shown to have a high viral concentration[6,22]. There are non-specific hypodense CT brain lesions likely representing infarcts or encephalitis[26] and brain atrophy particularly in the basal ganglia and subcortical white matter[6,17,22].

MR imaging is useful in primarily excluding occult disease not detected on CT imaging. Furthermore, the typically symmetrical T2 hyperintense periventricular while matter disease is best appreciated on MRI[11,22,25].

Progressive Multifocal Leuko-encephalopathy (PML).

In 4-7% of HIV-infected patients[25,26], infection with the J-C virus is associated with progressive white matter inflammation and demyelination known as progressive multifocal leukoencephalopathy (PML)[22]. The CT scan may be normal or show patchy asymmetrical and typically non-enhancing periventricular lesions. The pathognomonic subcortical U-fibre involvement and the occipito-parietal distribution of the lesions is best visualised on MRI[25].

HIV related vasculopathy

Vasculitis manifests commonly in HIV infected patients[8,12,17,23,26] and is typically associated with infarcts, resulting in either an acute ischaemic event or progressive dementia. Fungal infections may cause mycotic aneurysms resulting in haemorrhagic strokes[9,22,23] and associated ring or nodular enhancing lesions are an important imaging feature[23,26].

1.2.3. HIV/AIDS related neoplastic disease.

Non-Hodgkin high grade B-cell primary lymphoma is the most common primary neoplastic disease in AIDS patients, occurring in 5-7% of cases worldwide[17,24]. It is an AIDS defining illness and is more common than secondary lymphoma of the CNS[22,26].

It is usually a patchy enhancing solitary or multifocal periventricular mass with extensive immediate oedema involving the corpus callosum and crossing the midline[17,24]. It may be indistinguishable from toxoplasmosis[30] on CT imaging and MR spectroscopy demonstrates choline overproduction which is not a feature of toxoplasmosis and a useful differentiating characteristic[28].

1.3. Neuroimaging in confused HIV-infected patients

Whilst clinically isolated confusion occurs in up to 50% of HIV infected patients[10,22], focal neurological disease has been established in 40-70% of post mortem cases[17,22]. The presence or absence of neurological symptoms in these patients varies[17], and due to superior diagnostic capabilities, MRI is the preferred imaging modality in neuroAIDS regardless of the presentation[11,17,31].

CT imaging can be unreliable in conditions such as PML or HAND and the multi-sequences capabilities of MRI can be utilised to great effect to distinguish these

diseases. Similarly, diseases such as toxoplasmosis can be indistinct from tuberculoma, granular neurocysticercosis or even enhancing cryptococcomas[23]. The multiplicity and distribution of these often occult lesions is better visualised on MRI, thus improving the accuracy of diagnosis[22,28].

Furthermore, unlike CT, MRI does not utilise ionising radiation. Instead the body is subjected to a magnetic field and the hydrogen molecules found in specific body tissues emit signals that are sampled and converted to radiological images[19]. This is advantageous in settings of repeated imaging such as with these chronically ill patients[11,32].

The use of specialised MRI functions such as spectroscopy is limited by the poor availability of software and skilled MRI radiographers[11,28,33], but it may be useful in determining the metabolic characteristics (and therefore the pathological nature) of ambiguous neurological lesions.

CT is the mainstay of neuroimaging in both locally and foreign conducted studies[7,8,12,34]. Sewchuran (2013) found abnormality in 81% of the patients. These findings were similar to those of Schutte[8] (84%), Byanyima[34] (75%) and Berhe[7] (77%). In both Schutte and Sewchuran, the predominant abnormalities were non-mass lesions constituting more than 78% and 68% of the cases respectively. However, in Berhe[7] only 20% of patients had non-mass lesions.

The categories of space occupying lesions were not specified in Sewchuran (2013)[12] and Schutte (2013)[8], whereas Berhe[7] determined 80% of these were toxoplasmosis on CT. TB meningitis was the most prevalent non-mass lesion in 58% of patients according to Schutte[8], whereas focal and surface infections existed in 27% of patients Sewchuran[12].

There were patients with focal neurological deficits in all the cited studies (Table 1.1), however in Sewchuran[12] a significant cohort (58%) had no neurological symptoms. The findings between the two cohorts established neurological

symptoms are a poor predictor of CT findings. This is contrary to the findings by Byanyima[34], however this study had no comparable non-neurological cohort.

Only 5 (five) patients had MRI in Berhe et al[7], and of these only 2 (two) had both MRI and CT imaging. The findings of this cohort were not apparent in the study report. In an MRI-based study in Australia, Kwan et al (2014)[25] established that immune reconstitution syndrome (IRIS) is the predominant (10 – 40%) finding in HIV infected patients with focal neurological fallout. Toxoplasmosis accounted for 10% of the MRI findings.

Table 1.2: Comparison of Neuroimaging Studies in HIV / AIDS									
Study	**Study Type**	**Population**	**Modality**	**Abnormal**	**Normal**	**Confusion**	**Focal Neurological Deficit (+)**	**Focal Neurological Deficit (-)**	**Other Infomation**
Sewchuran 2013 (South Africa)[12]	Retrospective	156 56% M 44% F mean age 39 yrs	CT Pre/Post	68% - NMLs 4% - SOLs 9% (other) = 81%	19%	Yes	(n = 66) 86% had abnormal CTs 14% had normal CTs	(n = 90) 78% had abnormal CTs 22% had normal CTs	Neurological symptoms a weak predictorof abnormal CT
Schutte *et al* 2013 (South Africa[8]	Retrospective	128	CT Pre/Post	78% - NMLs 8% - SOLs = 84%	14%	Yes	n = 128	nil	
Byanyima *et al* 2015 (Uganda)[34]	Retrospective	151 mean age 34,6	CT Pre/Post	75% abnormal CTs	25%		n= 151	nil	Focal neurology is related to abnormal CT.
Berhe *et al* 2012 (Ethiopia)[7]	Retrospective	132 mean age 34,6 yrs	CT Pre/ Post MRI	57% - SOLs 20% - NMLs = 77%	23%	GCS records in 24,5%	unkown	unkown	80% of SOLs were toxoplasmosis
Kwan *et al* 2014 (Australia)	Retrospective		MRI	40% IRIS , 10% Toxo , 7% PML ,5% Lymphoma.					

1.4. Aims and Objectives

1.4.1. Aims

The aim of the research is to establish the common MRI brain findings in HIV positive adult patients presenting with confusion, who previously had a CT brain scan performed.

1.4.2. Objectives

- To determine the proportion of abnormal MRI brain scans in confused HIV infected adult patients
- To determine the common mass and non-mass radiological diagnoses
- To determine the MRI findings in patients with a normal prior CT brain
- To categorise the MRI findings in patients with or without associated neurological symptoms

2. Materials and Methods

2.1. Research Design

This research was a retrospective descriptive review of MRI and CT brain scans of HIV-infected adult patients presenting with confusion who also had a prior CT brain scan.

2.2. Study Setting

The study population was HIV positive adults at Helen Joseph Hospital Radiology Department, presenting with confusion for which they had CT and MRI brain between 1 October 2015 and 31 March 2017.

The Hospital is equipped with:

- a 16 Slice Phillips Brilliance MDCT Scan, Eindhoven, The Netherlands
- a 1,5T GE MRI Scan, Waukesha, WI, USA

2.3. Inclusion Criteria

- Confused HIV/AIDS patients who underwent an MRI brain examination following a prior normal or abnormal CT brain
- Only adult patients (18 years old and above) were included in the study

2.4. Exclusion Criteria

- Illegible request forms
- MRI scans done after 21 days of the CT scan

2.5. Data Collection

The data consists of CT and MRI brain images and was collected as follows:

- Patient MRI brain scan requests submitted and performed during the study period were reviewed and those that fulfilled the study inclusion criteria selected
- Only requests of patients with a clinical history of confusion or a subnormal GCS were included.
- The qualifying patients' HIV statuses were confirmed from ELISA tests conducted by the National Health Laboratory Services (NHLS).
- The actual MRI and CT images of the qualifying patients were reviewed and those done 21 days or more apart were excluded.
- The included MRI and CT scans were then copied into digital storage devices.
- The MRI and CT images of each patient were randomly allocated numbers corresponding to their unique Data Collection Sheet (Appendix B),
- The CT and MRI scans were allocated to two qualified Radiologists (Dr Nikelo Mabandla and Dr Tanusha Sewchuran) who interpreted the CT and MRI scans according to the customized report format (Appendix B)
- Abnormal scans were broadly reported into mass and non-mass lesions, which were further classified into radiological diagnoses.
- The mass or non-mass radiological diagnosis interpreted by the radiologists constituted data points.

The demographics and presence or absence of focal neurological symptoms were recorded in the Data Collection Sheet

2.6. Data Analysis and Statistics

- To determine the proportion of abnormal MRI brain scans in confused HIV infected adult patients
- To determine the common mass and non-mass radiological diagnoses
- To determine the MRI findings in patients with a normal prior CT brain
- To categorise the MRI findings in patients with or without associated neurological symptoms

Microsoft Excel was used to capture data and STATA software, version 13.0 (StataCorp, College Station, Texas) was used for data management and analysis. Sociodemographic characteristics of patients included sex, age and race.

Objectives 1 through 3 were achieved using frequency tables and percentages for categorical covariates, mean and standard deviation (median and inter quartile range) for continuous variables. Pie charts were also used to portray the distribution of categorical factors.

Objective 4 was achieved with the use of Pearson chi-square test to determine any association between MRI findings and the presence or absence of associated neurological symptoms. A multinomial model was also used to test the likelihood of MRI findings in patients with or without neurological symptoms. Marginal plots were used for demonstrating data analyses.

2.7. Ethics

The Human Research Ethics Committee (HREC) of the University of the Witwatersrand approved the study (Certificate M170232), and site approval was also obtained from the Helen Joseph Hospital Medical Advisory Committee. The approval certificate is attached as Appendix C.

3. Results

3.1. Demographics

In the period of 01 October 2015 to 31 March 2017 there were 341 MRI brain scans performed at Helen Joseph Hospital. Of these 112 (33% of total population) were for confirmed or suspected HIV infected patients. 107/341 (31%) patients had had a CT scan done at Helen Joseph Hospital (five were unverified) and in 103 /341 (30%) patients the MRI and CT scans were performed within 21 days (mean 7 days). There was a documented clinical presentation of confusion in 87 patients (26%), however HIV infection was confirmed in **77** (23%) and this constituted our study population. Of these 67 (87%) had reported focal neurological symptoms and 10 (13%) had not.

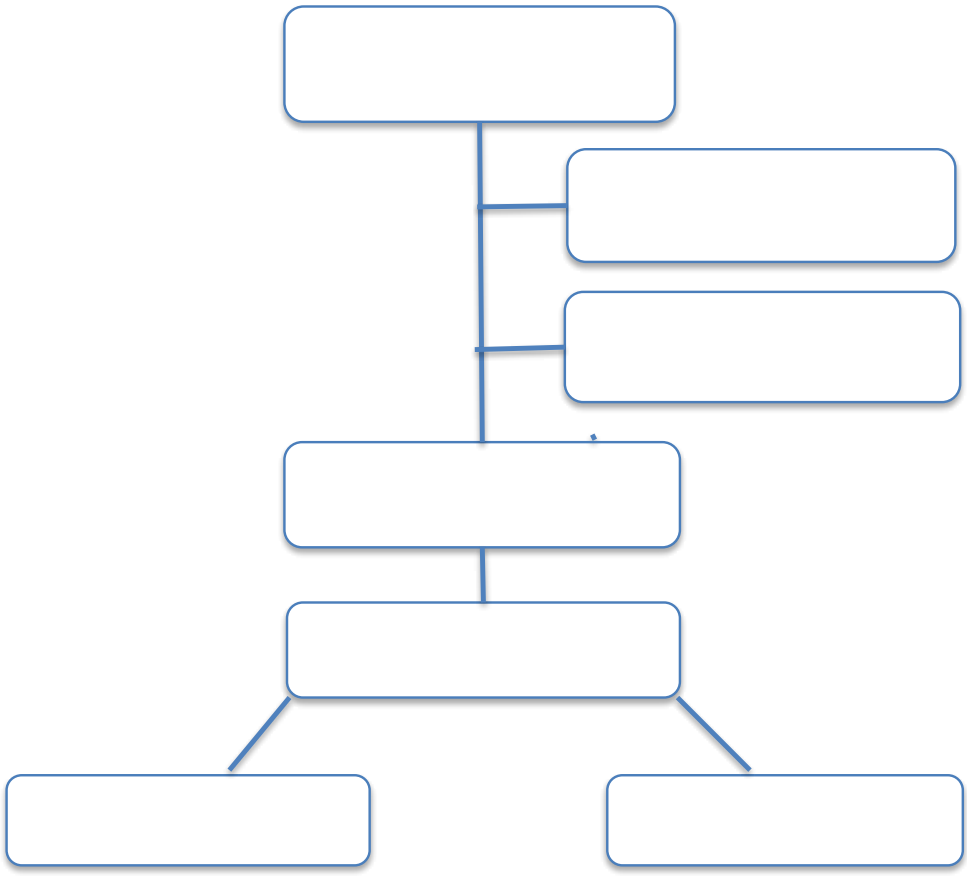


Figure 3.1: Flowchart of Population Sampling

Table 3.1 below represents the sociodemographic characteristics of the study participants. Of the 77 patients included in the final sample, 37 were males, representing 48% of the patients, and 40 were females representing 52%.

Table 3.1 : Demographic characteristics of HIV-infected confused patients

Characteristics	**Frequency (%)**
Age (mean, sd)	41 (12.2)
Sex	
Male	37 (48%)
Female	40 (52%)
Race	
Black	63 (82%)
White	4 (5.2%)
Indians	4 (5.2%)
Coloured	6 (7.8%)

Figure 3.2 below portrays the distribution of these demographic characteristics. We found that on average females were statistically significantly younger (*p*-value: 0.04). More than 80% of patients were black, and the female participants were relatively and statistically significantly younger, mean: 38,5 years vs. 44,1 for men (sd.: 13).

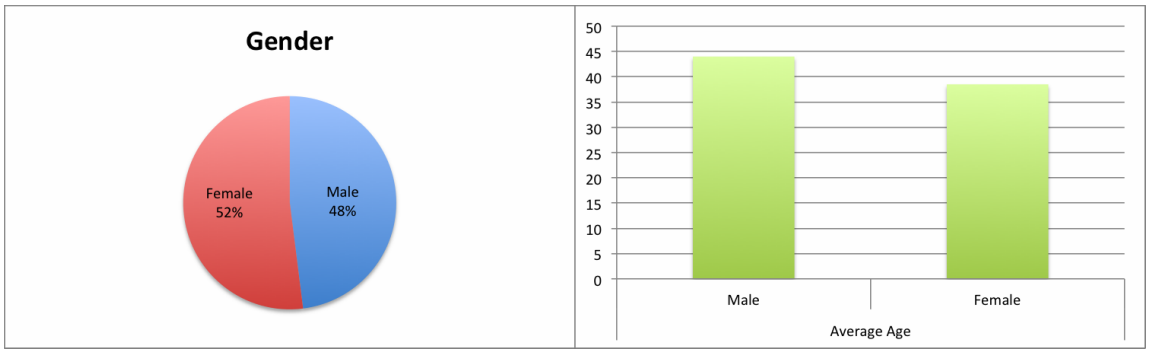


Figure 3.2: Distribution of patients

3.2. CT and MRI Scan Findings

Findings from both the CT and MRI brain scans were categorised into normal, SOLs (space occupying lesions) and NMLs (non-mass lesions). Results from the two modalities were then compared in order to determine the agreement between MRI and the CT findings.

We found that 57/77 (74%) of the MRI scans were abnormal and 20/77 (26%) were normal as demonstrated in Table 3.2 and Figure 3.3. Of the abnormal MRI scans the commonest finding was NMLs in 37/77 (48%) of patients, whereas SOLs occurred in 20/77 (26%) of the cases. The CT scans were normal in 23/77 (30%) and abnormal in 54/77 (70%). Among the abnormal cases 34/77 (44%) were NMLs, with 20/77 (26%) identified as SOLs.

Table 3.2: CT and MRI findings in confused HIV-infected patients with confusion.

Finding Category	CT	MRI
	N (%)	N (%)
Normal findings	23 (30)	20 (26)
SOL (Space Occupying Lesions)	20 (26)	20 (26)
NML (Non-Mass Lesions)	34 (44)	37 (48)



Figure 3.3: Distribution of the CT and MRI findings.

Table 3.3 shows the distribution of the initial CT findings across the different MRI categories. We established a significant difference between the distributions. (Fisher's exact: *p*-value = 0,001).

Of the 23 normal CT scans, the MRI confirmed 14 (61%) as normal (this constitutes 18% of the total study population). The MRI detected abnormality in 9 (39%) of these patients (11% of the total population).

	Normal	Abnormal
CT	23	0
MRI	14	9

The Cohen Kappa analysis (k=0,68) indicated a substantial agreement. Further analysis of this cohort is made in Table 3.5 below.

Of the 20 normal MRI scans, there was a stastically significant high prevalence of normal (14 = 70%) or NMLs (6 = 30%) findings on CT scans. None (0%) of the CT SOLs were normal on MRI (Chi-square and Fisher exact: *p*-value: 0,001).

Table 3.3: Fit of CT vs. MRI Findings in confused HIV-infected patients

	MRI Category			Total
	SOL	NML	Normal	
Normal CT	2	7	14	23
	8.70	30.43	60.87	100.00
	10.00	18.92	70.00	29.87
SOL	18	2	0	20
	90.00	10.00	0.00	100.00
	90.00	5.41	0.00	25.97
NML	0	28	6	34
	0	82.35	17.65	100.00
	0	75.68	30.00	44.16
Total	20	37	20	77
	25.97	48.05	25.97	100.00
	100.00	100.00	100.00	100.00
Fisher's exact = *p*-value : 0,001				

The sensitivity of CT vs MRI was 85,7% and the specificity 57% meaning whilst CT is reasonably able to correctly pick up patients with neurological disease it is not as able to exclude those without.

Table 3.4 below provides a full description of the findings by each modality in the total population of 77 HIV infected patients presenting with confusion. For both CTs and MRIs, the NML category was bigger than the SOL and normal categories.

HIV encephalitis / HAND was the most prevalent MRI diagnosis in 15 (19,5%) cases. CVA followed this in 10 (13%) and PML with 7 (9%) of cases. CT showed a similar pattern with 20 (26%) HAND cases, and 6 (8%) CVA cases.

Primary and secondary brain neoplasia was detected in 10 (13%) CT cases and in 7 (9%) MRI scans. Primary CNS lymphoma and glioblastoma multiforme (GBM) was detected in 5 cases (6,5%) with both CT and MRI scans.

Metastatic disease was detected in 5 (6,5%) of the CT cases, with better characterisation this decreased to 2 cases (2,6%) following the MRI scans. TB granuloma manifested in 5 (6.5%) of both CT and MRI cases.

Table 3.4: MRI and CT Findings in confused HIV-infected patients

Description	**MRI n (%)**	**CT n (%)**
Normal	**20 (26)**	**23 (30)**
SOLs	**20 (26)**	**20 (26)**
PCNSL	3 (4)	2 (2.6)
CNS Toxoplasmosis	4 (5.2)	3 (4)
TB granuloma/abscess	3 (4)	3 (4)
Cystic Disease	1 (1.3)	1 (1.3)
GBM	2 (2.6)	3 (4)
Mets	2 (2.6)	5 (6.5)
Pit. Macroadenoma	1(1.3)	1 (1.3)
Meningioma	2 (2.6)	1 (1.3)
Lipoma	1(1.3)	1 (1.3)
Dermoid	1 (1.3)	
NMLs	**37 (48)**	**34 (44)**
PML	7 (9)	4 (5.2)
Meningitis	2 (2.6)	2 (2.6)
HIV Encephalitis / HAND	15 (19.5)	20 (26)
CVA	10 (13)	6 (7.8)
ADEM	2 (2.6)	2 (2.6)
MS	1 (1.3)	

As demonstrated in Table 3.5 below average age of patients with normal CT scans was 41 years, and 56.5% were females and 69.5% (16/23) had focal neurological symptoms and 39% (9/23) also had abnormal MRI scans.

Table 3.5: Summary of Normal CT Scans in confused HIV infected patients

	Sex	Age	Focal Neurology	MRI Diagnosis
1	F	35	Yes	HAND
2	F	30	No	Normal
3	F	25	No	HAND
4	F	46	Yes	Normal
5	M	45	Yes	HAND
6	F	30	Yes	Normal
7	M	32	Yes	Normal
8	F	47	Yes	CVA
9	F	32	No	Normal
10	M	56	Yes	Lymphoma
11	M	26	Yes	Normal
12	F	55	Yes	ADEM
13	F	42	Yes	Normal
14	M	55	Yes	CVA
15	M	46	No	Normal
16	M	38	No	Normal
17	F	55	No	Normal
18	M	48	No	Normal
19	M	50	Yes	Normal
20	M	36	Yes	Normal
21	F	42	Yes	MS
22	F	23	Yes	Normal
23	F	55	Yes	Dermoid

3.3. MRI Findings and Focal Neurology

The MRI findings were further classified according to the presence or absence of neurological symptoms. Table 3.6 and Figure 3.4 below show neurological symptoms were recorded in 94,6% (35/37) 90% (18/20) and 70% (14/20) of patients with NMLs, SOLs and normal MRI scans respectively.

The association between these MRI findings and the presence or absence of neurological symptoms was significant (Pearson Chi-square: *p*-value = 0.028, Fisher's exact 0,032).

Table 3.6: MRI Findings vs. Focal Neurological Signs

MRI Categories	Focal Neurology		Total
	Absent	Present	
	N (%)	N (%)	
SOL	2 (10) (20)	18 (90) (27)	20 100.0 (26)
NML	2 (5.5) (20)	35 (94.5) (52)	37 100.0 (48)
Normal	6 (30.0) (60)	14 (70.0) (21)	20 100.0 (26)
Total	10 (13) 100.00	67 (87) 100.00	77 100.00 100.00
Pearson Chi-square = *p*-value : 0,028, Fisher's exact = *p*-value: 0,032			

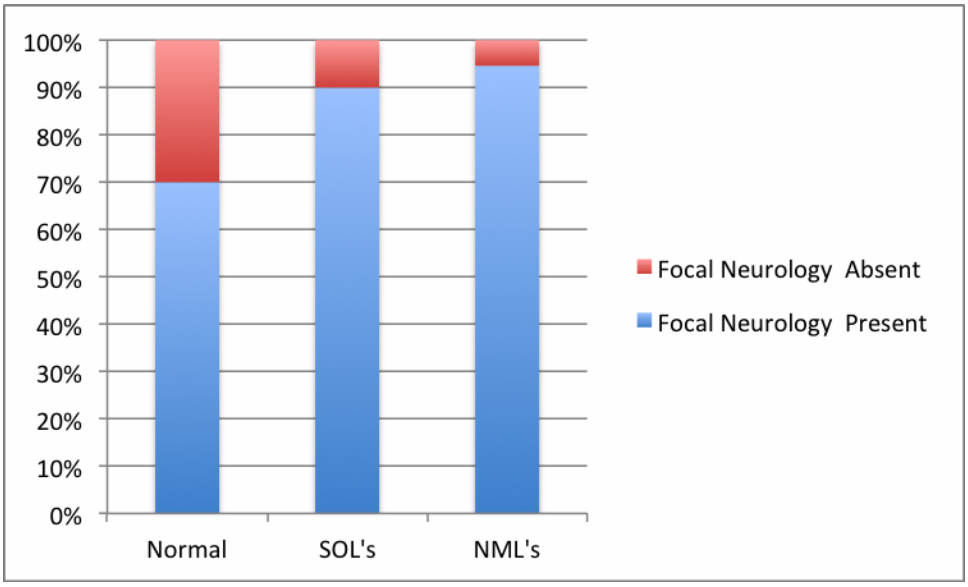


Fig 3.4: MRI Findings vs. Focal Neurological Signs

Table 3.7 below shows CT and MRI findings by presence or absence of focal clinical neurology.

Table 3.7: Distribution of Normal MRI Findings.

	Focal Neurological Deficit	
	Present N (%)	Absent N (%)
CT Normal	8 (40)	6 (30)
CT Abnormal	5 (25) – HAND 1 (5) - Meningitis	0
	Focal abnormality (n= 55)	No focal abnormality (n= 67)
CT	40 (73)	25(27)
MRI	NMLs 35 (52) SOLs 18 (27)	14 (21)

A multinomial logistic regression was performed to predict MRI findings in the presence or absence of focal neurological symptoms. The results were plotted separately in figures 3.4, 3.5 and 3.6 below.

Figure 3.5 shows there is higher likelihood of SOLs in patients with neurological symptoms (marginal probability: 0.26; 95%CI), compared to those with no symptoms (margins 0.20; 95% CI). However, as shown the 95% confidence intervals completely overlap, rendering the test between the two groups not statistically significant.

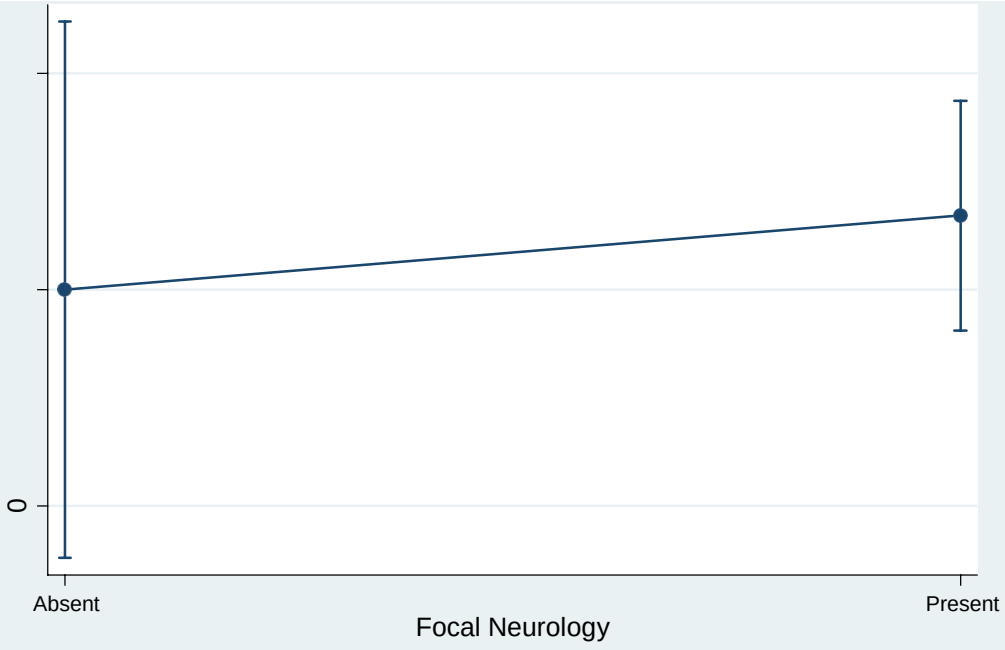


Fig 3.5: Prediction of SOL by Focal Neurological Signs

We also found a high likelihood of NMLs in patients with neurological symptoms compared to those with no neurological symptoms. (Figure 3.6).

This finding was statistically significant (margins effect: 0.52, *p*-value: 0.001), implying that patients presenting with neurological symptoms are more likely to have NMLs.

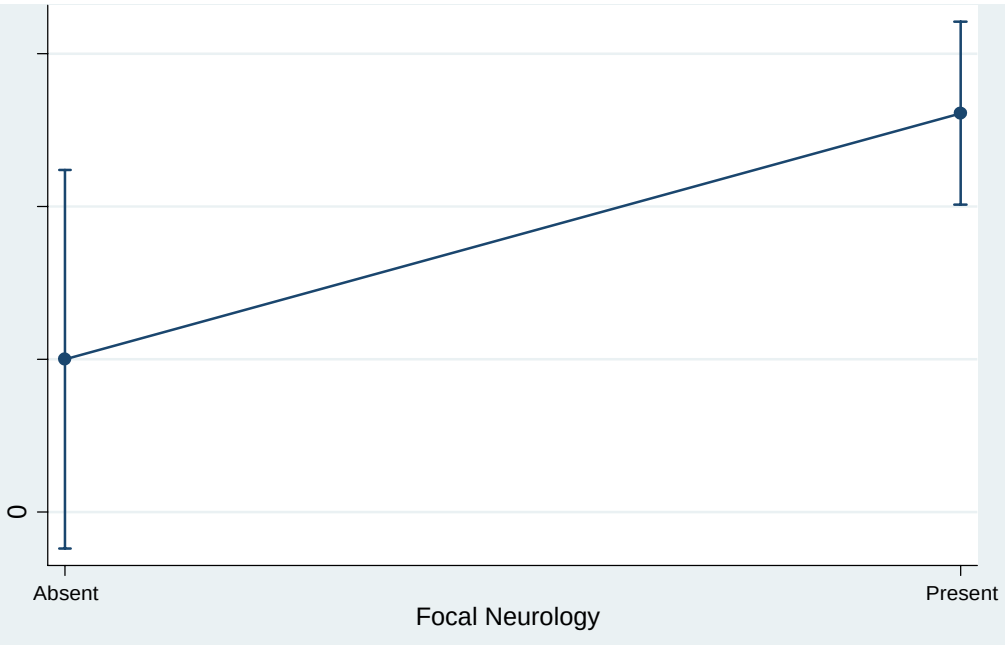


Fig 3.6: Prediction of NML by Focal Neurological

Lastly, Figure 3.7 shows that patients with neurological symptoms are less likely to have normal MRI findings compared to patients with no neurological symptoms (margins 0.21, *p*-value: 0.001 for both normal and abnormal MRI).

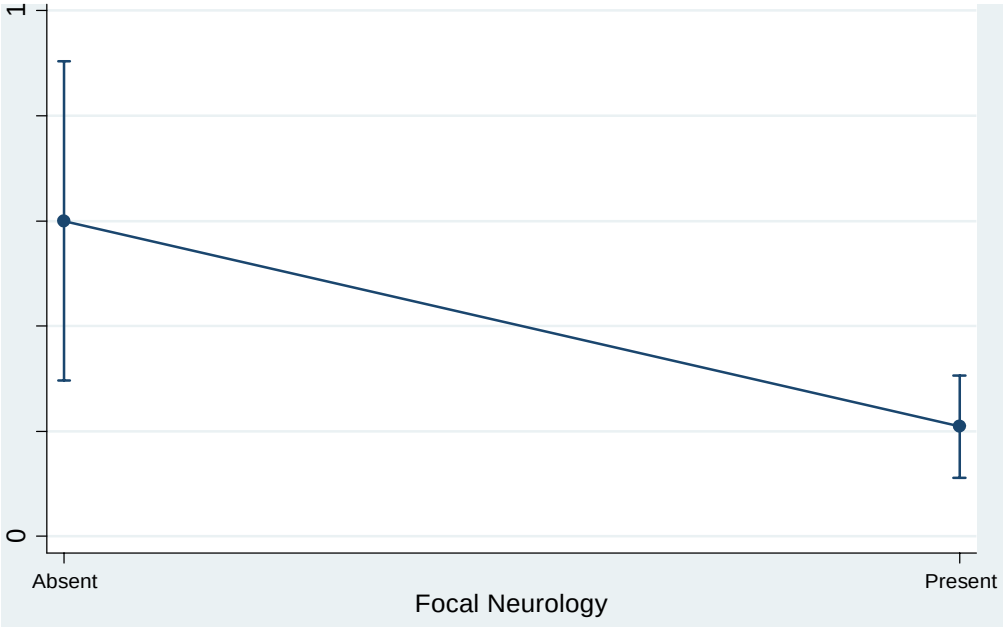


Fig 3.7: Prediction of Normal MRI by Focal Neurological Signs

4. Discussion

The aim of this study was to understand the role of MRI in the neuroimaging of confused HIV-infected patients. This study's premise was that most MRI requests are made subsequent to either an inconclusive CT scan result or a normal scan in the setting of a clinically confused patient. In a resource constrained environment such as ours it is important, for the purposes of developing clinical indications and streamlining scanning lists, to understand the implication of focal neurological signs in confused HIV infected patients. This study investigated the usefulness of additional urgent or elective MRI in the context of HIV associated confusion.

To determine this we compared the findings on both CT and MRI in 77 patient presenting to the radiology department with confusion, and compared these findings in subpopulations with and without focal neurology.

The association between the specific MRI findings (SOLs, NMLs or normal) and the presence or absence of focal neurology was tested using logistic regression.

4.1. Facilities

MRI is an expensive and scarce resource in South Africa. In Johannesburg there are five MRI scans within the public healthcare sector. Two of these are stationed at Chris Hani Baragwanath Academic Hospital and one each at Charlotte Maxeke Johannesburg Academic Hospital and the Helen Joseph / Rahima Moosa Mother and Child Academic Hospital Complex.

About 1,6m (12,5%) of Gauteng's population is HIV positive[35,36], and besides the related burden of disease, our imaging service caters for a high level of trauma related morbidity and increasing incidence of non-communicable disease.

We established that of the total MRI brain scans performed during the study period 33% were for suspected or confirmed HIV infected patients and of these, 96% had undergone CT brain scan within the previous 21 days (mean 7 days). Furthermore, 26% of total HIV infected population presented with confusion - slightly lower than the 30% documented in a previous prevalence study of the same patient population at the same institution (Sewchuran[12], 2013). This is most likely because in the clinical context, some patients only had CT scans performed and were thus not included in the study

4.2. Results in Context

4.2.1. Demographics

The mean age of our study participants was 41 years. This was slightly higher than 39[12] and 34,6[7] years in the studies by Sewchuran (2013) and Berhe (2012). This likely related to the increase in life expectancy[36] post-ARV rollout in the South African public healthcare system. Also, in contrast to Sewchuran (2013), our study had more male (52%) than female (48%) participants.

In this study, 74% of the total population had abnormal MRI scans in comparison to 70% of CT scans, at variance with the 81% in Sewchuran (2013)[12] and is likely influenced by the study design, including the different study population.

Significantly more NMLs were detected on MRI than CT (48% vs. 44%) (Chi –square and Fisher exact *p*- value: 0.001). This suggests that the improved spatial resolution of MRI enhances the diagnosis of non-mass lesions, in agreement with Senocak (2010)[26] and the American College of Radiology (ACR) guidelines[11].

HIV encephalitis / HAND was the most prevalent finding constituting 19,5% of the patients. This mirrors the 16% pre-ARV treatment era prevalence in South Africa (Cross, 2013)[29]. The current local prevalence is 5%[29a], and is likely related to the freely available ARV treatment.

Cerebrovascular disease (CVA) was present in 13% of MRI patients. Skiest et al (2002)[17] and Senocak et al (2010)[26] and Schutte (2013)[8] documented stroke in 8% of HIV infected patients. The prevalence of HIV-vasculitis related CVA remains an interesting area of future research.

The MRI diagnosis of PML was made in 9% of the patients in this study. This is slightly above the 4-7% incidence reported by Skiest (2002)[17], Senocak (2010)[26], Kwan (2014)[25]. The

incidence is typically highest in patients with a CD4 count less than 100. We, however, did not document the CD4 count of study participants as part of this study.

CNS toxoplasmosis was confirmed in 5% of cases, well below 10% (Kwan, 2014)[25] or 15 – 50% (Senocak, 2010)[26] and 37 – 45% (Berhe, 2013)[7]. Because CNS toxoplasmosis typically occurs in severely immunosuppressed people, the advent of ARVs may be an important factor in the currently lower prevalence of the disease.

TB granuloma / abscesses were radiologically diagnosed in 4% and leptomeningitis in 2,6% of our patients. Follow up data on response to treatment has however not been acquired. The radiological prevalence of TB neurological disease remains unclear and is low in non-South African studies. However, Schutte (2013)[8] showed mortality of up to 56% from TB meningitis in HIV infected patients and Marais (2014)[37]reported that TB accounted for more than half of meningitis cases in the HIV positive population in 2011. It is important to note that CT and correlation with lumbar puncture biochemistry is typically sufficient to diagnose meningitis, and as such those patients would not qualify to be included in our study population.

The MRI diagnosis of Primary CNS lymphoma (PCNSL) was made in 4% of the patients. This is comparable to 4-7% according to Skiest (2002)[17] and 2-5 % in Kwan (2014)[25].

We demonstrated 23 (30%) of the CT scans were normal, in contrast to 19% in Sewchuran[12]. Of the 23 normal CT scans, 14 (61%) were also normal on MRI, representing 18% of the total study population). The pathology seen in the remaining 9 abnormal MRI's were HIV encephalitis/ HAND (13%), CVAs (9%) and isolated cases of ADEM, multiple sclerosis, a dermoid and lymphoma.
This suggests that MRI is more sensitive to the detection of HAND, CVAs and white matter disease than CT.

70% of patients with focal neurological symptoms had a normal CT, , and of these 50% were normal and 50% were abnormal on MRI. Importantly all patients presenting without focal neurology had a normal MRI – suggesting an association

between a normal CT and a normal MRI in patients in this context. To our knowledge this is the first time this has been reported and behoves further clinical/radiological correlation.

In our study 87% of the total population had focal neurological signs. This is in contrast to Sewchuran[12] (42% of total population). Skiest (2002) established focal neurology in 40-70% of these patients[17]. Of the cohort with focal neurology, 79% had abnormal MRI scans (52% NMLs and 27% SOLs), 76% had abnormal CT scans, lower than the 86% reported by Sewchuran (2013)[12]. This is most likely related to the study design – not all patients with CT scans underwent an MRI.

There was a significant association between abnormal MRI findings, particularly NML's, and the presence of focal neurological signs (as demonstrated in Table 3.6 above, Chi-Square *p*-value: 0,028 and Fisher's *p*-value: 0,032). This is in agreement with the study by Sewchuran[12]. However, our study demonstrated that the presence of focal neurology was a significant predictor of NML's and not of SOL's (Figs 3.4 and 3.5), in contrast to Sewchuran (2013)[12].

We also found that whilst 40% of patients with no focal neurology had abnormal MRI scans, the absence of focal neurology (Fig. 3.6) was a strong predictor of a normal MRI *(p*-value: 0,001). This is a significant finding and contradicts the inconclusive CT-based findings of Sewchuran[12]. Although this is cohort was small in our study, in both modalities the proportions are lower than in Sewchuran[12]. Notably all 60% with normal MRI scans also had normal CTs. This suggests that a normal CT may be sufficient to exclude pathology in these patients – in keeping with our regression analysis that patients with no focal signs are more likely to have normal MRI's (Fig 3.6).

4.2.5. Table of Comparison

Table 4: Comparison between our Study and other related Studies

Study Name	Design	Sample Size	Confusion	Abnormal Findings		Normal	Focal Neurology				Other
				CT	MRI		Present (n=67)		Absent (n=10)		
							CT	MRI	CT	MRI	- Focal neurology a good predictor of abnormal MRI. - Normal CT ass. with normal MRI in absence of neurology.
Our Study	Retrospective (CT and MRI)	77	100%	HAND: 26% Masses: 13% CVA: 8%	HAND: 19,5% CVA: 13% PML: 9%	30% - CT 26% - MRI	Abnormal 76% Normal 24%	79% 21%	30% 70%	40% 60%	
Sewchuran	Retrospective (CT)	156	100%	Atrophy: 47% Infection 27% Focal Lesion: 23% CVA: 20%		19%	CT Abnormal 86% Normal 14%		CT Abnormal 78% Normal 22%		Focal neurology a weak predictor of abnormal CT
Berhe *et al*	Retrospective (CT)	132	24,5%	Toxo: 45% Other SOLs: 11% CVA: 10% Meningitis: 4% HAND: 4%		22%					80% of SOLs were toxoplasmosis
Kwan *et al*	Retrospective		Unknown		IRIS: 40% Toxo: 10% PML: 7% Lymphoma5%						

4.3. Current Applications

The findings of our study confirm that MRI neuroimaging statistically significantly alters the diagnoses ascribed to HIV infected patients, thus potentially changing their management.

We found that in confused patients without focal neurology and a normal CT, the MRI is also likely to be normal and its usage was therefore less warranted.

We also demonstrated that focal neurological signs are strongly associated with non-mass lesions on MRI. We therefore recommend additional MRI in patients with suspected non-mass lesions on CT.

4.4. Limitations of the Study

This was a retrospective descriptive study and potentially qualifying participants were excluded due to insufficient records. Whilst confusion was confirmed in 87 (26%) of the patients, laboratory confirmation of HIV infection was obtainable in only 77 (23%) cases.

The study was designed to include patients who had underwent both CT and MRI scans. This did somewhat limit the selected disease spectrum. For example, of the 112 potentially qualifying, CT scans couldn't be confirmed in 5 (4%) of the patients either because they were scanned elsewhere or the images were lost.

The waiting times between the CT and the MRI were not standardised and patients with a waiting time beyond 21 days between scans were excluded. In our study 103 of the 107 confused HIV infected patients had CT and MRI scans done within the 21 days of one another and the average time in between scans was 7 days.

The presence or absence of confusion and focal neurological symptoms is largely dependent on the experience of the referring clinician. Lastly, it also at the clinician's discretion to determine which patients warrant MRI scanning.

4.5. Further Research

Our study was confined to confused patients who had had CT of the head. A larger sample population, incorporating all HIV infected patients, could accrue more information.

We demonstrated that all the patients who had no neurological symptoms and a normal CT scan had a normal subsequent MRI. However this was a small number and a study of a larger group may yield valuable insights.

Lastly, the spectrum of HIV related spinal cord lesions remains unknown and determining these would be useful particularly in patients with focal neurology.

5. Conclusion

In this study we determined that MRI was abnormal in the majority (74%) of confused HIV infected patients who had undergone a prior CT scan. We demonstrated that non-mass lesions, particularly HAND, were the predominant finding, particularly if in the presence of focal neurological signs.

In resource-constrained centres such as ours it is therefore recommended that in confused HIV infected patients MRI should be performed in patients with focal neurological symptoms and suspected non-mass lesion/s on CT. However, in patients with no focal neurology and a normal CT scan a supplementary MRI scan is not recommended.

Appendix A: The Glasgow Coma Scale[20]

Glasgow Coma Scale		
BEHAVIOUR	**RESPONSE**	**SCORE**
Eye Opening	Spontaneous	4
	To Speech	3
	To Pain	2
	No Response	1
Best Verbal Response	Orientated to Time, Place and Person	5
	Confused	4
	Inappropriate Words	3
	Incomprehensible Sounds	2
	No Response	1
Best Motor Response	Obeys Commands	6
	Moves to Localised Pain	5
	Flexion Withdrawal from Pain	4
	Abnormal Flexion (Decorticate)	3
	Abnormal Extension (Decerebrate)	2
	No Response	1
TOTAL	Best Response	15
	Comatose	8 or less
	Totally Unresponsive	3

Appendix B: Data Collection Sheet

Data Collection Sheet (Patient No:…..)		
Characteristics		**Code***
Sex	**Male**	**0**
	Female	**1**
Race	**Black**	**1**
	White	**2**
	Indians	**3**
	Coloured	**4**
Focal Neurological Symptoms	**Present**	**1**
	Absent	**0**
	Not Known	**9**
CT Scan normal		
(0)		**0**
Abnormal CT (SOLs)		
(1)	**CNS Toxoplasmosis**	**2**
	Abscess	**3**
	Cystic Disease	**4**
	Other SOL (specify)	**5**
Abnormal CT NML's	**PML**	**6**
(2)	**Meningitis**	**7**
	HIV Encephalitis	**8**
	Atrophy	**9**
	Other NML (specify)	**10**
Abnormal MRI (SOL's)	**PCNSL**	**11**
(3)	**CNS Toxoplasmosis**	**12**
	Abscess	**13**
	Cystic Disease	**14**
	Other SOL (specify)	**15**
Abnormal MRI (NML's)	**PML**	**16**
(4)	**Meningitis**	**17**
	HIV Encephalitis	**18**
	Atrophy	**19**
	Other NML (specify)	**20**
MRI Scan normal		
(5)		**21**

*Code: excel spreadsheet statistical data point

Appendix C: Ethics Approval Letter

REVISED

R14/49 Dr N Mabandla

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170232

NAME: (Principal Investigator)	Dr N Mabandla
DEPARTMENT:	School of Clinical Medicine Division of Radiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	MRI findings and use in confused HIV infected patients
DATE CONSIDERED:	24/02/2017
DECISION:	Approved unconditionally
CONDITIONS:	Additional supervisor and project title change approved on 31 August 2017
SUPERVISOR:	Drs N Mahomed & T Sewchuran
APPROVED BY:	CB Penny 1/9/2017 Professor CB Penny, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	24/04/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially reviewed in **February** and will therefore be due in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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