Imaging of neurocysticercosis and the influence of HIV

Marianne Kuehnast

A research report submitted to the University of the Witwatersrand, Johannesburg in fulfilment of the requirements of the degree of Master of Medicine 2016/2017.

DECLARATION

I, Marianne Kuehnast, declare that this research report is my own work. The research report is submitted for the degree of Master of Medicine- Radiology at the University of the Witwatersrand. It is submitted in a 'submissable for publication' format with my protocol and an extended literature review and has not been submitted before for any degree or examination at this or any other institution.

……

Date:……...

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ABSTRACT

Background: The effect of HIV infection on the evolution of NCC constitutes a new area of interest.

Purpose: To review the literature on the imaging appearances of NCC and HIV co-infection and compare it with our cases.

Materialsand methods: Data from both published andlocal cases were analysed. HIV-infected cases were divided into "low" (<200 cells/mm^3) and"high" (≥200 cells/mm^3)CD4 groups. These groups were compared and the effect of treatmentwas evaluated.

Results: Thirty-three cases were evaluated - 20of our, and 13 published, cases. The published cases had parenchymal brain cysts, whereas our cases had both parenchymal and subarachnoid cysts (p=0.0050). The published cases also had intra-axial cysts, whereas our cases had both intra- and extra-axial cysts (p=0.012). The published cases had predominantly cystic lesions, whereas our cases had both cystic and granulomatous lesions (p=0.019). There were no differences between cases with a CD4 count of <200 cells/mm^3 and cases with a CD4 count of ≥200cells/mm^3but, interestingly, 3% of the cases with a CD4 count of <500cells/mm^3,compared with 50% of the cases with a CD4 count of ≥500cells/mm^3,had racemose cysts.

Conclusion:NCC is very prevalent in South Africa and may complicate the diagnosis and treatment of patients with concomitant HIV infection.Patients with a "low" CD4 count may present with atypical lesions, delaying the diagnosis of NCC. Early

initiation of HAART may result in patients presenting with more classical symptoms and imaging appearances, thus improving outcomes.

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ABBREVIATIONS

3D-CISS	Three-dimensional (3D) constructive interference in steady state
ADEM	Acute disseminated encephalomyelitis
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
DNA	Deoxyribonucleic acid
EITB	Enzyme immunotransfer blot
ELISA	Enzyme-linked immunosorbent laboratory assay
GRE	Gradient recalled echo
FLAIR	Fluid-attenuated inversion recovery
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
IRIS	Immune reconstitution inflammatory syndrome
MCA	Middle cerebral artery
MeSH	Medical subject headings
MRI	Magnetic resonance imaging
NCC	Neurocysticercosis
PCR	Polymerase chain reaction
PDWI	Proton density-weighted imaging
RNA	Ribonucleic acid
STIR	Short TI inversion recovery
TB	Tuberculosis
WHO	World Health Organisation

Chapter 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1Rationale

Cysticercosis is endemic in South Africa and many other developing countries. Neurocysticercosis is common in these countries and results in significant morbidity with seizures and in some cases with complications such as hydrocephalus. The imaging findings of neurocysticercosis are well described on both CT and MRI.

However, the effects of immunosuppression on the evolution of the parasite, and incidence of complications are a new area of interest due to the prevalence of co-infection with HIV. These variable changes in the organism behaviour may well affect the imaging appearances, which are often reflective of vitality of the organism and the inflammation associated with it. In addition the degree of immunosuppression may result in variable appearances or degrees of visibility. The endemic regions for cysticercosis infection and HIV overlap and we expect the prevalence of patients demonstrating co-infection to increase.

We aim to review the literature relating to the effects of HIV on the appearances of neurocysticercosis on MRI and CT and present the collated findings and with related evidence. We will also include our own collected cases in the analysis.

1.2Epidemiology

Taenia Solium is a parasitic worm (helminth) responsible for neurocysticercosis (NCC) infection. This parasite is responsible for the largest proportion of parasitic infections of the central nervous system (CNS).

Cysticercosis is a disease of the developing world. The location, number and size of the cysticercal lesions determine a patient's clinical presentation. The clinical presentation, prognosis and outcome are also influenced by the host's immune status.

Twenty- seven percent of HIV-infected patients in South Africa, who present with neurological symptoms as a result of concomitant infection are co-infected with NCC. In South Africa and other areas with a high prevalence of NCC, co-infection with HIV is becoming more common. Despite this fact, very little is known about the presentation, imaging findings, treatment and outcome of patients infected with NCC as well as HIV [1].

Imaging is critical to the diagnosis of NCC and these findings are widely published. However, unusual forms and appearances of NCC may occur more frequently in patients with HIV-infection due to uncontrolled parasitic growth [2]and suppressed features of inflammation because the host's immune response is altered.

1.3Pathogenesis

Pigs are the intermediate host of the *Taenia Solium* parasite, and human beings may serve as either the definitive or the intermediate hosts. Human beings become the definitive host of the adult tapeworm by acquiring viable cysticercus larvae from pork. In contrast, ingestion of embryonated Taenia eggs (oncospheres) deposited on faecally contaminated food or self- contamination converts a human into the intermediate host. In this latter scenario, cysticerci are found in any organ, but preferred sites of implantation are the brain (NCC), muscles, skin, and eyes[3].

The cysts consist of a wall and a scolex. The wall of the cyst does not elicit an inflammatory response by the host, as long as it is intact [4,5].

Intra-axial cysts (ie found in the brain parenchyma) are usually <10 mm in diameter. They are most commonly found at the grey/white matter interface or in the basal ganglia.

Cysts in extra-axial locations such as the subarachnoid spaces, sylvian fissure and basal cisterns may grow to >10cm in size because their growth is not restricted by pressure from the brain parenchyma [4].

Cysts with a scolex are referred to as *Cysticercus cellulosae*, and cysts proliferating without a scolex are referred to as *Cysticercus racemosus*, but this can be confusing if both forms coexist in the same patient. NCC encephalitis is seen more commonly in younger patients and in women and is caused by the presence of a massive number of cysts with associated inflammation. However, the converse is also true, with some patients tolerating a high load of intraparenchymal cysts and not experiencing any significant symptoms [4].

1.4Imaging of NCC without HIV

1.4.1 Clinical features

Taenia Solium may cause disease of the CNSin the following ways: the cysts may cause mass effect or obstruction, the cysts may elicit an inflammatory response in the form of oedema, or the death of the parasite may result in residual scarring in the form of fibrosis, granulomas and calcification [5].

According to Del Brutto et al, a definitive diagnosis of cysticercosis is made with one absolute criterion, or with two major criteria plus one minor criterion and one epidemiologic criterion. There are three absolute criteria, namely

- pathologic demonstration of the parasite
- cystic lesion with a scolex found on CT or MRI
- direct visualisation on fundoscopy[6]

On the basis of clinical presentation, cerebrospinal fluid (CSF) analysis and imaging findings, NCC can be classified into either active or inactive forms. Arachnoiditis and vasculitis are regarded as active forms of the disease [5]. Children with NCC infection usually present with a single lesion and have relatively mild symptoms, compared to adults. Extraparenchymal NCC is rarely found in children[7].

NCC is diagnosed through a combination of clinical findings, immunology and imaging findings. Immunology in the form of NCC-specific IgG antibodies can be detected in either the serum or the CSF[8].Both CT and MRI can be used for detecting lesions, and both modalities are highly sensitive and specific. However, CT is superior to MRI for the detecting of calcified granulomas, whereas MRI has better contrast resolution for the better detecting of intraventricular lesions as well as inflammatory changes such as oedema [5].

1.4.2Imaging findings according to the stage of evolution

The stage of evolution of the parasite determines the MR-imaging features of NCC. Cysticercosis in the brain has a natural course, consisting of four stages [4].Imaging

findings in each stage reflect underlying changes in the disease process and the host response[3].

In the initial stage, the embryo is non-cystic and often invisible on CT and MRI. During the stages of early development from embryo to larva, focal non-enhancing areas of oedema may be seen that in a few months progress to small, homogenously enhancing lesions. These lesions are thought to correspond to tissue invasion by the larvae and a secondary inflammatory response[3].

A small, marginal nodule is seen to project into a clear cyst in the vesicular stage. This marginal nodule is the larva of the parasite. The cyst does not elicit an inflammatory reaction and the larva dies within four to five years if the infection is not treated. Mature cysts are readily apparent on CT and MRI and measure 5-20mm. Cysts are common at the grey/white interface, but are also seen in the basal ganglia, the cerebellum, and the brainstem. On MRI, the cyst is round with an iso- or hyperintense mural nodule (scolex) relative to white matter on T1W image (the fluid content of the cyst is low signal). On T2W images, the scolex can be iso- or hyperintense and can be obscured by high- signal-intensity cystic fluid. The scolex is therefore better seen on proton density-weighted images (PDWI)[3]. There is no oedema or ring/discoid enhancement associated with the cysts in the vesicular stage. The fluid within the cyst is isointense to CSF on all sequences, except on 3D-CISS (a three-dimensional high-resolution heavily T2-weighted sequence in steady state)[4]The 3D- CISS sequence helps to identify the cyst wall, cyst fluid and scolex.

The sequence is of a very high resolution and it accentuates the difference in T2 characteristics between the CSF and the fluid within the cyst. The cyst therefore appears relatively hypointense to the surrounding CSF [9].

The larva begins to degenerate in the colloidal vesicular stage and this is seen as ring/ discoid enhancement and oedema on MRI. The contents of the cyst have a high signal relative to CSF on T1WI, PDWI, FLAIR and T2W because of the proteinaceous fluid and debris that has accumulated in the cyst [4].A hyperintense cyst surrounded by hyperintense parenchymal oedema is therefore typical of the colloidal vesicular stage. Diffuse encephalitis may occur (especially in children) during this stage, and especially after the use of oral antihelmintic agents, requiring large doses of corticosteroids in order to control brain oedema[3].

The lesions retract and start to mineralize in the granular nodular stage. There may still be associated oedema and the lesions may appear as either enhancing nodules or micro-ring-like lesions.

The final stage in the evolution of the parasite is the nodular calcified stage, during which the calcified granulomas are seen to ‘bloom’ on gradient-echo (GRE) or susceptibility- weighted imaging (SWI) [4].

In summary, viable, non-degenerating cysts display neither ring/discoid enhancement nor surrounding oedema, whereas degenerating cysts are characterized by ring/discoid-enhancement and surrounding oedema. Calcified granulomas represent

inactive or dead larvae [6]. Contrast/gadolinium-imaging is therefore recommended, as are mineral-sensitive sequences such as GRE and SWI.

1.4.3*Ventricular neurocysticercosis*

The second- most common site of NCC is the ventricular system. More than 54% of patients with intracranial NCC were found to have this form of the disease. Due to their high protein content, these cysts are usually hyperintense relative to CSF on T1WI. Usually there is no scolex, but if there is one, it is hyperintense on T1WI and does not enhance on post-contrast imaging. The cyst is usually free to move inside the ventricle, and can cause ventriculitis presenting as a subependymal reaction, as well as acute hydrocephalus[4,10]. 'Brun's syndrome' is characterised by intermittent foramen obstruction caused by free-floating cysts. In such a case, the patient will present with episodic recurrent headaches, vertigo, ataxia and drop attacks[11].

1.4.4*Unusual/atypical forms of NCC*

Unusual/atypical forms of NCC include subarachnoid, spinal, orbital and intraparenchymatous lesions as well as reactivation of a previously calcified NCC [4,10].

Cisternal-subarachnoid involvement is estimated at 3.5% of all NCC, making this the third-most common site[4,10].Cellulose cysts are usually located only intra-axially, whereas racemose cysts are usually larger and multiloculated, resembling "bunches of grapes", and are usually found in the basal cisterns [11]. The cystic masses do not enhance post gadolinium but cause cisternal expansion and deformity[4,10]. These

cysts usually lack a scolex[3].Local inflammatory reaction can cause leptomeningeal thickening, fibrosis and focal calcifications. Infarction can be caused by vasculitis, because the perforating vessels are affected [4,10].NCC cysts have been reported in the cerebellopontine cisterns, and even in the adjacent auditory canal [4].

NCC may involve the spinal space and/or the spinal-cord CSF in fewer than 1% of cases. Spinal lesions may be intradural-extramedullary (54%), intramedullary (17%) or both (17%). Extradural involvement is rare. Diffuse intradural-extramedullary cysticercosis may result from direct CSF dissemination from a cerebral source. Subarachnoid disease manifests as intradural-extramedullary cysts or arachnoiditis[9]. Intramedullary cysticercosis (IMC) results from haematogenous dissemination and is extremely rare. Lesions may be ring-enhancing, single cysts expanding the cord or may present as a multiloculated cystic mass[3]. NCC-related hydrocephalus, meningitis and the use of anti-epileptics and antihelminithics predispose to spinal-cord involvement[12].

Orbital NCC via the choroid vessels can cause retinal detachment, retinal perforation, vitreous invasion with inflammation and blindness (or can be extraocular in nature)[10].

Atypical NCC includes miliary and pseudotumoural forms.Miliary NCC is rare and is caused by a massive cyst load, spread throughout the brain parenchyma, resembling a “starry sky”.

Another atypical presentation is one that is indistinguishable from primary or secondary tumours. Yet another rare presentation is the reactivation of a calcified lesion with surrounding oedema (‘target lesion’)[10].

1.5HIVinfection and NCC

Currently, there is no evidence to suggest that HIV infection exacerbates NCC, or vice versa. [13].It is reasonable to assume that immunocompromised patients are unable to rid their bodies of the parasite owing to an impaired humoral immunity. These patients are therefore more likely to develop more severe NCC than patients with a competent immune system.

Unusually severe forms and presentations have been seen in patients with haematological malignancies, suggesting that a decreased immunity may well have an effect on both the evolution and the lifecycle of the parasite [13,14].

HIV infection may also affect the clinical course of cysticercosis. When the parasite is in its cystic stage, the symptoms of NCC are more dependent on the cell-mediated immunity of the host than on the presence of the parasite itself [14].

A chronic immune response occurs in patients who are immunocompetent – because of multiple cell types, including plasma cells, B- and T- lymphocytes, macrophages and mast cells. These inflammatory cells secrete both inflammatory and anti-inflammatory (Th1 and Th2) cytokines.

NCC results in seizures because of the inflammatory response to the parasite’s antigens that are released when the parasite dies [5].

Because HIV-infected patients may have a deranged immunological response to disease, HIV makes the serological detection of NCC unreliable[8,15]. Significantly fewer patients with concomitant HIV infection will have a positive serology, compared with immunocompetent patients. This is probably because HIV-positive patients are unable to mount a significant enough response against the parasite because of a weakened immunity[15].

Having a low CD4 count/ depressed immunity appears to have a “protective effect” in that these patients are less likely to be symptomatic compared to those patients with a high CD4 count. Patients with lower CD4 count tend to present with atypical lesions [1].Immunological testing in the form of either electroimmunotransfer-blot assay (EITB) or enzyme-linked immunosorbent assay (ELISA) must be carefully interpreted and must always be considered in conjunction with the clinical as well as the radiological findings [15].

In patients with HIV- infection, the cysticercosis lifespan may be longer because these patients have a less effective immune-inflammatory response. Also, the immune response in HIV-infected patients declines with the progression of the disease.

Antihelminths have been advocated for use in patients infected with both HIV and parenchymal NCC in order to try to achieve quicker results [13].

1.6 **Imaging of NCC in HIV-infected patients**

An impaired cell-mediated immunity results in atypical cysts in the form of giant or racemose cysts. This probably occurs because the growth of the parasite is uncontrolled. According to Serpa et al, these findings are supported by only 30 cases of concomitant HIV and NCC reported in the literature[1].

1.6.1*Differential diagnosis of a 'ring-enhancing lesion' in an HIV-infected patient*

Intracranial lesions are common in HIV-infection and are more frequently seen in advanced stages of the disease (i.e. low CD4 counts). These lesions may be due to opportunistic infections, neoplasms or cerebrovascular diseases. Specifically, opportunistic infections of the brain are more likely when the CD4 count is <200 cells/mm3[16].

In a series by Modi et al, 6 patients with NCC and HIV co-infection who presented for imaging had a mean CD4 count of 509 cells/mm3 (range, 107-768 cells/mm3). Other etiologies predominated in patients with substantially lower CD4 counts[17].

Toxoplasmosis presents with multiple 'ring-enhancing lesions' with an eccentric nodule on imaging. Toxoplasmosis is the most likely cause of focal neurologic signs, presenting with multiple ring- enhancing brain lesions on imaging.

Primary CNS lymphoma is the second-most common cause of intracranial mass lesions in HIV-infected patients. On CT, these primary lymphoma masses are hyperdense or isodense, round or oval, with approximately 50% of them being multifocal ring-enhancing lesions.

Infective causes of multiple ring-enhancing lesions in HIV-positive patients include the following: tuberculosis, cryptococcus, syphilis, candida and neurocysticercosis. Metastases and cerebrovascular diseases should also be considered in the differential.

NCC cysts may sometimes be difficult to distinguish from tuberculomas, even in patients not co-infected with HIV. Tuberculomas are usually larger than NCC cysts and tend to be >2cm in diameter. They also tend to have an irregular margin, whereas NCC cysts have smooth margins, and tend to elicit greater mass effect and cause progressive focal neurological deficits, which NCC usually does not do. It is not easy to diagnose TB on CSF because the cultures and polymerase chain reaction (PCR) for *Mycobacterium Tuberculosis*have a very low sensitivity [16].

In countries where the endemic areas of cysticercosis and HIV- infection overlap, it is obvious that the imaging diagnosis of single and multiple ring-enhancing lesions is becoming difficult. Adding to this is the fact that HIV-infected patients with low CD4 counts may have NCC with lesions that do not demonstrate ring enhancement.

1.6.2IRIS

NCC may be paradoxically worsened by an inflammatory reaction occurring after the initiation of HAART[14], a condition termed ‘immune reconstitution inflammation syndrome’ (IRIS). IRIS is likely to occur when the initial CD4 count is low, and the HIV viral load is high. Once HAART is started, IRIS is more likely to develop - the faster the improvement in the CD4 count and the faster the drop in the HIV viral load [1].

There are no case reports documenting specific cases of patients with Neuro-IRIS associated with NCC, and very few review articles make mention of this specific entity[1,14]. Imaging appearances of NCC in these circumstances, however, would be classical because of the immune response of the host.

1.7Medical Management

NCC responds very well to antihelminth therapy, whether the patient has concomitant HIV or not. The response rate is 85%. However, a lower complication rate and a lower rate of symptom presentation may be attributable to a weaker inflammatory response to the dying organisms after the administration of cysticidal drugs or because the neurological symptoms resolved after specific treatment was instituted for other CNS infections besides NCC. There is, however, a high case fatality rate (12%) associated with HIV-positive patients compared with HIV-negative patients[18].

Empiric anti-toxoplasmosis therapy for two weeks is suggested for patients who present with brain lesions in areas where NCC is not endemic. In such cases, toxoplasmosis and primary CNS lymphoma are the most likely causes of the lesions. If there then is no response to treatment, a stereotactic brain biopsy is recommended. In developing countries, where TB and NCC are more prevalent, presumptive therapy is started first before resorting to a brain biopsy. As mentioned previously, clinical presentation in NCC is more likely if the CD4 count is high[8].

1.8Aim

We aim to review the literature relating to the effects of HIV on the appearances of neurocysticercosis on MRI and CT and present the collated findingswith related evidence. We will also include our own collected cases in the analysis.

1.9Objectives

1. To conduct a review of the published literature on imaging appearances of NCC and the effect of HIV co- infection on imaging**.**

2. To describe the CT and MRI findings of published cases of NCC and HIV co-infection.

3. To describe the CT and MRI findings of 20 cases of NCC and HIV co-infection presenting to Chris Hani Baragawanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital.

4. To determine, if any, significant difference in the CT and MRI findings of the two groups.

5. To pool the two groups together and then to determine, if any, significant differences in the CT and MRI findings in relation to "high" and "low" CD4 counts.

6. To describe the treatment administered and the outcomes of treatment.

1.10Methods

A literature review will be performed, extracting data from the following databases and search engines: Medline/PubMed, Scopus, Sciencedirect and Google. The search term *neurocysticercosis* will be pairedwith each of the following: *imaging*, *HIV*, and *spine*,using the Boolian operator "AND". Synonyms (*cysticercosis, MRI, CT)* will be

employed according to database-specific preferences, and terms will be linked to medical subject headings (MeSH) in Medline/PubMed. Bibliographies of relevant articles and "grey" literature from the Google search will be examined.

All English-language journals will be reviewed in full, and all foreign-language journals will have their abstracts reviewed. Review articles will be accessed, but are not expected to yield data and will be used mainly for acquiring background information and additional references.

1.10.1 *Data Collection*

Information will be extracted relating to the imaging appearances of neurocysticercosis on CT and MRI into "high" (CD4≥200) and"low"(CD4<200) CD4-count groups in patients who are HIV-infected.

Patient imaging data from publications regarding the appearance of NCC on MRI and CT in HIV-infected patients will be extracted and collected under the following headings - imaging modality (CT/MRI), location (parenchymal/racemose; anatomical location), number of lesions (single/multiple), size (small/large/giant), presence of a mural nodule, enhancement characteristics (ring/discoid), consistency (cystic or solid), based on MRI signal intensity or density on CT, inflammatory response (surrounding oedema), associated findings (hydrocephalus/infarct/others), immune competence - CD4 <200 (low) /≥200 (high). [See appendix 1]

We will try to collect about twenty of our own cases of NCC and HIV. These imaging cases will be obtained from the radiology records. The files of these patients will then be sourced from the hospital records.

1.10.2Data Analysis

The data will be analysed to compare the frequencies of each imaging finding of the "low" CD4 group (<200) with those in the "high" CD4 group (≥200).Fisher's exact test will be used and the help of a statistician will be sought. [See appendix 2]

1.11Ethics

Permission was obtained from the research ethics committee of the University of the Witwatersrand (ethics no M131175).

1.12Timeline (2015- 2016)

	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug
Literature review									
Preparing protocol									
Protocol assessment									
Ethics application									
Collecting data	X	X	X	X					
Data analysis			X	X					
Writing up thesis			X	X					
Writing up paper			X	X					

1.13Funding

Accessing publications, stationary, and photocopying	R2000
Transport	R1000
Statistician	R2500
TOTAL	R5500

1.14References

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Source	MRI or CT	Parenchymal or (racemose) cisternal / subarachnoid	Location: frontal etc.	Single or multiple	Small or large (<2cm) or (≥2cm)	Presence of mural nodule (Ca++ or not)	Ring / discoid enhancement	Cystic appearance (CT or MRI) (Vesicular or colloidal)	Oedema	Other findings e.g. hydrocephalus or infarct	CD4 count Low (<200) High (≥ 200)

Appendix 1

Variable	Low CD 4 Count (≤200 cells/mm^3)	High CD 4 Count (≥200 cells/mm^3)
Imaging modality -MRIonly -CT only -MRI and CT		
Parenchymal or subarachnoid -Parenchymal (brain) only -Racemose (cisternal) only -Both Parenchymal and Racemose -Ventricular lesions (in addition to other lesions) -Intramedullary lesions (amongst other lesions)		
Location (some patients had multiple locations) -Parenchymal (Brain lobe) -Diffuse -Brainstem -Lumbar epidural -Intramedullary -Lateral ventricles -Cisterns -Sylvan fissure		
Single or multiple -Single -Multiple		
Small/Giant -Small -Giant -Small and Giant		
Mural nodule -Enhancing -Ca++ -None		
Enhancement -Ring enhancement -With and without enhancement -Discoid enhancement -No enhancement -Not available		
Cystic/ Solid -Cystic -Solid		
Oedema -Surrounding oedema -None -Not available		
Associations **No associations**		

Appendix 2: Comparison of patients with low CD4 counts (CD4<200) and patients with high CD4 counts (CD4≥200)

CHAPTER 2: SUBMISSABLE ARTICLE

Full Title:

Imaging of Neurocysticercosis and the influence of HIV

Authors:

Marianne Kuehnast [1, 2*], Savvas Andronikou [3, 4], Tebogo Linda Hlabangana [1, 2] Colin Nigel Menezes [2, 5].

Affiliations:

[1] Department of Radiology, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa.

[2]Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

[3]Clinical Research and Imaging Centre, University of Bristol, United Kingdom.

[4]Department of Radiology, Bristol Royal Hospital for Children, United Kingdom.

[5]Division of Infectious Diseases, Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa.

[*]**Corresponding author:**

Marianne Kuehnast

Department of Radiology

Chris Hani Baragwanath Academic Hospital

Faculty of Health Sciences

University of the Witwatersrand

Chris Hani Road, Soweto

Johannesburg, South Africa

Email: drmkuehnast@gmail.com

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Full Title:

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ABSTRACT

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Purpose: To review the literature on the imaging appearances of NCC and HIV co-infection and compare it with our cases.

Materialsand methods: Data from both published andlocal cases were analysed. HIV-infected cases were divided into"low" (<200 cells/mm^3) and "high" (≥200 cells/mm^3)CD4 groups. These groupswere compared and the effect of treatmentwas evaluated.

Results: Thirty-three cases were evaluated - 20of our, and 13 published, cases. The published cases had parenchymal brain cysts, whereas our cases had both parenchymal and subarachnoid cysts (p=0.0050). The published cases also had intra-axial cysts, whereas our cases had both intra- and extra-axial cysts (p=0.012). The published cases had predominantly cystic lesions, whereas our cases had both cystic and granulomatous lesions (p=0.019). There were no differences between cases with a CD4 count of <200 cells/mm^3 and cases with a CD4 count of ≥200cells/mm^3but, interestingly, 3% of the cases with a CD4 count of <500cells/mm^3,compared with 50% of the cases with a CD4 count of ≥500cells/mm^3,had racemose cysts.

Conclusion:NCC is very prevalent in South Africa and may complicate the diagnosis and treatment of patients with concomitant HIV infection.Patients with a “low” CD4 count may present with atypical lesions, delaying the diagnosis of NCC. Early initiation of HAART may result in patients presenting with more classical symptoms and imaging appearances, thus improving outcomes.

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Introduction

South Africa has the highest prevalence of human-immunodeficiency-virus (HIV) infection in the world[1]. In 2014, an estimated 10.2% (5.51 million) of the total population were HIVinfected[2]. Twenty-seven percent of HIV-infected patients present with neurological symptoms as a result of concomitant infection with neurocysticercosis (NCC). Research on NCC has however been limited and has been referred to as a "neglected" tropical disease by the WHO [3].

Imaging is critical to the diagnosis [4]. However, unusual forms and appearances of NCCmay occur in patients with HIVinfection.Imaging features may be due to uncontrolled parasitic growth[5] and suppressed features of inflammation because of the host's altered immune response.

The effect of immunosuppression on the evolution of the parasite and the incidence of complications constitute a new area of interest. Immunosuppression affects the behaviour of the organism and the imaging appearances,reflecting the vitality of the organism and associated inflammation. The degree of immunosuppression may result in variable appearances and degrees of visibility.

The purpose of this study was to describe both the effects of suppressed immunity from HIV co-infection on the imaging appearances of NCC and the effects oftreatment by reviewingour cases andpreviously published imaging data.

Materials and methods

Data were extracted from Medline/PubMed, Scopus, ScienceDirect and Google. Search-term combinations paired the term *neurocysticercosis* with each of the following: *imaging*, *HIV* and *spine*,using the Boolean operator "AND". Synonyms (*cysticercosis, MRI, CT)* were employed according to database-specific preferences, and terms were linked to medical subject headings in Medline/PubMed.

Imaging data from MRI and CT in HIV-infected patients were extracted and collected under the following headings: imaging modality (CT/MRI), location (parenchymal, subarachnoid, ventricular or spinal),specific anatomical location, size (small/giant), presence of a mural nodule (calcified or not), enhancement characteristics (ring/discoid), inflammatory response (surrounding oedema), presence of calcified granulomas (stage 4/inactive form), associated findings(hydrocephalus/infarct/others), and immune competence (CD4 <200 cells/mm^3["low"]/≥200 cells/mm^3["high"]).

Published cases

Inclusion criteria: Patients had to be HIVpositive and have concomitant NCC. Only cases with a CD4 count were included.Imaging findings had to be described, or the actual images had to be available for review.If the patient had only calcified granulomas (stage 4) on imaging, the serology had to be positive.

Exclusion criteria: Cases where imaging findings were recorded only in a simplified format or by means of a table were excluded, unless the original case report/series could be retrieved to obtain the imaging findings. Patients were excluded if the diagnosis was questionable.

Our cases

Cases were collected over a period of five years from the radiology recordsof two teaching hospitals (Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital). Images were analysed retrospectively.Same criteria wereapplied. Imaging diagnosis had to be clear and response to treatment was regarded as a confirmation of the diagnosis.Files were retrievedfrom the hospital records and original reports of all images were re-analysed.Permission was obtained from the research ethics committee of the University of the Witwatersrand (ethics no M131175).

Data analysis

Based on the inclusion and exclusion criteria, the sample size of 13 published cases and 20 of our own cases were included in this study.

Data were analysed to compare the frequencies of each imaging findingofthe "low" CD4 group (<200 cells/mm^3) with those in the "high" CD4 group (≥200 cells/mm^3).A cut-off value of 200 was used because a CD4-count value of <200 is AIDS-defining [6].

Analysis SAS® 9.4 statistical software package (SAS Institute, Inc., Cary, North Carolina) was used.Fisher's exact test was usedfor analysingthe imaging findings,and the Wilcoxon rank sum testfor analysing the range and distribution of CD4 counts.A significance-level setting of 5% (p-values <0.05)was used.

Definitions

Parenchymal lesionsare lesionsin the brain parenchyma and brainstem, but not spinal cord.Subarachnoid lesionsare lesionsin the surface sulci or in the basal cisterns.

Racemose cysts refer to a cluster of cysts(“bunch of grapes”) in the subarachnoid space of the brain or spinal cord. These cysts lack a scolex and have little/no associated oedema.

Spinal lesionsmay be intramedullary, intradural-extramedullary (subarachnoid) or extradural.Brainstem lesionsrefer to lesions in the midbrain, pons or medulla.

Intra-axiallesions includelesions in both the brain parenchyma and the intramedullary spine, whereas extra-axial lesions include lesions in both the subarachnoid (surface sulci and basal cisterns) and the intradural-extramedullary and extradural spaces in the spine.

Calcified granulomas represent stage-4 or inactive disease. To be included in the study, a patient needed to alsohave active disease (cysts) or positive serology.

Small cystsare <2cm in diameter, whereas giant cystsare regarded as being>2cm in diameter.

Cysts with mural nodules are pathognomonic for NCC. Giant and racemose cysts by definition do not have mural nodules.

Enhancementmay be ring or discoid. Usually extra-axial, giant and racemose cysts are not characterised by significant enhancement.

We made a note of associated neurological complications only.

Results

Of the published cases, only 13 (table 1) had both detailed imaging findings and a CD4 count so that a comparison could be made and were included in the study. Data of 20 patients from our institutional records were collected (table 2)to produce a total of 33 cases for analysis (table 3).

Demographics

The mean age of thepublished cases was 42 years, whilst that of our cases was 37 years.Majority of the cases were male.Two of the published cases were of African, 7 of Latin American and 4of Indian descent.All our patients were African.
Overall, the median CD4 count of the 33 cases was 180 (IQR 105-396).

Clinical presentation

Patients with cerebral lesions presented with headaches, signs of raised intracranial pressure or seizures. Those with spinal lesions presented with focal neurological deficits. Only 3 cases presented with signs and symptoms of probable immune-reconstitution inflammatory syndrome (IRIS) after follow-up (table 4 and 5).

Imaging modality and imaging findings

Generalfindings in both the published and our cases (n=33)

In approximately 46% (n=15) of thestudy sample (n=33) the lesions were located in the brain ie (both parenchymal and subarachnoid); 6% (n=2) had ventricular lesions; 9% (n=3) had racemose lesions; 15% (n=5)in the spine;15% (n=5)in the brainstem and15% (n=5)in the cisterns.

Most patients (49%) had both intra- and extra-axial lesions. Whilst most patients (29 of the 33 cases) in the study presented with multiple lesions, only 4 (12%) presented with single lesions. The majority of the patients (73%) had only small cysts.

Forty-two percent of the patients had calcified granulomas, whereas 58% of them had only cystic lesions.Sixty-one percent had mural nodules.

Sixty-seven percent of the patients had cysts displaying significant ring enhancement, and 42% had cysts with surrounding oedema.

When 4 patients with only extra-axial or only giant cysts were excluded from the analysis (n=29), 66% had mural nodules, 72% had cysts with significant ring enhancement and 48% had cysts with surrounding oedema. (The 4 aforementioned patients were excluded because both extra-axial and giant cysts by definition have neither mural nodules, ring enhancement nor surrounding oedema.)

Forty-nine percent of the patients had neurological associations.

Published cases vs our cases(see table 6)

All the published cases were imaged using MRI, compared with 6of our patients. Fourteenof our patients were imaged solely by means of CT.

Nine of the 13 published cases tended to presentwith parenchymal lesions. The other four cases presented with both parenchymal and subarachnoid lesions, whereas12 of our 20 casestended to present with both parenchymal and subarachnoid lesions in the same patient (p= 0.0050) (see graph 1)

Nine of the 13 published cases had predominantly intra-axial lesions, whereas 12 of our 20 cases tended to have both intra- and extra-axial lesions (p=0.012) (see graph 2)

Twelveof the 13 publishedcases tended to have only cystic lesions, whereas 12 of our 20 patients tended to have both cystic and granulomatous lesionsin the same patient (p=0.019) (see graph 3)

Five of our,compared with 4 of the publishedcases, had other co-infections,most often including toxoplasmosis (5 cases) and TB (3 cases). We were able to distinguish tuberculomas (patient 18) from NCC cysts -tuberculomas not being cystic,but largerand having irregular, enhancing walls.The CSF was also suspicious for TB. In our setting, toxoplasmosis is tested by means of serology and is treated empirically, especially if the CD4 count is low. Only 5 of the total of 33 cases had hydrocephalus as a complication.

One of our patients (patient 20) presented with typical findings of HIV encephalitis andhad a CD4 count of only 23 cells/mm^3.

*CD4 count of <500 vs CD4*count of ≥500

"Immunocompetent" was taken to have a CD4 count ≥500.A CD4 count of an uninfected adult/adolescent ranges from 500 to 1600 cells/mm^3 [6].Only 4 patients had CD4 counts ≥500, making it difficult to make accurate conclusions or inferences. There was however a significant association between the presence/absence of racemose lesions and the CD4 count (cut-off set at 500) (p=0.033). Three percent of those with a CD4 count of <500 had racemose lesions, compared with 50% of those with a CD4 count of ≥500.

"Low" vs "high" CD4 count(see table 3)

No statistically significant differenceswere noted between these two groups. The imaging features showing a tendency towards association with a "high" CD4 count (≥200 cells/mm^3), included ringenhancement (p=0.14) and oedema (p=0.17), but the differences were not statistically significant due to the small sample size. There may also be a tendency towards intramedullary location (2 out of 17 patients, or 11.8 %, in patients with a"low" CD4 count), but this was not statistically significant (p=0.73). Ventricular lesions were found only in patients with a "high" CD4 count (p=0.23).

Treatment and outcomes(see tables 7 and 8)

Only 2 out of the 16 cases in the "high" CD4-count and 2 out of the 17 in the "low" CD4-count group had their cysts surgically removed. Those4were all published cases.

One patient (patient 13) had a biopsy of a giant cyst, which helpedto significantly decreaseits size.

Sixteen casesreceived antihelminthictreatment only, of which onereceived neitherantihelminthicsnor surgical treatment and clinically improved. There was no evidence of 4of our cases of having received therapy.

In the “high” CD4-count group only 10 out of 14 cases were started on highly-active antiretroviral therapy (HAART), whilst in the “low” CD4-count group 8 out of 13 cases were started on HAART. Only 2 of the published cases,as opposed to7 of our patients, were not started on HAART.

Eleven out of 14 (79%) patients from the “high” CD4-count group improved completely after treatment, whilst the remainder still had residual symptoms at the time of discharge. However, only 6 out of 13 (46%) patients from the “low” CD4-count group improved, of which 1 (a published case) passed away in hospital. Sadly, many of our patients were lost to follow-up.

Three patients received empiric treatment for toxoplasmosis after imaging, whilst 1 of our patients was treated for ADEM and TB before imaging.

One of our patients from the “high” CD4-count group(patient 4) presented with imaging features of IRIS. After starting HAART, the patient’s follow-up imaging initially showed improvementfollowed by worsening, and then improvement again.

Discussion

Imaging plays a vital role in the diagnosis of NCC, whichrequires demonstration of the parasite - a cystic lesion with a scolex on either CT or MRI[4]. CT has a high sensitivity and specificity in most forms of NCC and is superior to MRI for calcified granulomas, whereas MRI has a much higher contrast resolution, resulting in better lesion conspicuity, detection of ventricular involvement and inflammatory changes[17].MRI findings are variable, depending on the stage of evolution of the infection. In South Africa, CT is more readily available because of the costsinvolved. In the public sector in the province of Gauteng, there are only 0.3 MRI units per million people, compared to 2.2 CT units per million people [18].

With HIV co-infection, it becomes more complex to diagnose NCC. Intracranial mass lesions are common and are frequently seen in advanced disease. These may be due to opportunistic infections (commonly TB and toxoplasmosis), neoplasms (primary CNS lymphoma) or cerebrovascular diseases[19].

In endemic areas where NCC and HIV infection overlap, the diagnosis of both single and multiple ring-enhancing lesions is more difficult, as findings are not typical. There is no evidence to suggest that HIV infection exacerbates NCC or vice versa[10]. It is reasonable to assume that immunocompromised patients are unable to rid the parasite due to impaired humoral immunity. Therefore they are more likely to develop severe NCC than patients with a competent immune system[8,10].HIV infection may also affect the clinical course. In the cystic stage, the symptoms are more dependent on the cell- mediated immunity than on the presence of the parasite itself[8].

Because HIV patients have a deranged immunological response, serological detection of NCC is unreliable [9,20]. Immunological testing in the form of an enzyme-linked immunosorbent assay (ELISA) must be carefully interpreted in conjunction with the clinical as well as the radiological findings [20].

The diagnosis of active NCC was based on typical imaging findingsand response to treatment. Serology was not helpful and was positive in only2 patients and indeterminate in 1 patient,although 9 of the published cases had positive tests.

There were interesting imaging differences between the published and our cases. Our cases tended to have both parenchymal and subarachnoid cysts in the same patient,whereas the literature cases tended to have parenchymal cysts ($p=0.0050$). Our cases also tended to have both intra- and extra-axial($p=0.012$) as well as both cystic and granulomatouslesions ($p=0.019$) in the same patient. Published cases tended to have only intra-axial and only cystic lesions in the same patient.

These findings may reflect the higher burden of NCC in South Africa and that our patients are possibly repeatedly exposed to, and become re-infected with, NCC.

Another explanation could be a different strain of cysticercosis in Africa that may result in a different clinical presentation. Two strains have been identified - one in Asia, and one in Latin America. The African *Taenia Solium* is thought to be similar to the one in Latin America, but the clinical manifestations of cysticercosis may differ or there may even be a particular genotype [21].

There was a significant association between the presence/absence of racemose lesions and the CD4 count when a cut-off value of 500 was used. Three percent of the patients with a CD4 count of <500 had racemose cysts, compared with 50% of those with a higher CD4 count.

One would expect a greater prevalence of racemose cysts with lower CD4 counts because of a lack of immunity and uncontrolled parasitic growth. Racemose NCC may also be attributed to a variety of cestodes, which could be either an aberrant *Taenia Solium* or a sterile coenurus of *Taenia Multiceps* or *Taenia Serialis* [22].

Imaging data from both our and the published cases suggest that there are some differences in appearance between caseswitha“high” CD4and cases with a “low” CD4 count.It is more likely for contrast enhancement and oedema to be present on imaging with a“high” CD4 count - perhaps because it allows for an immune response against a dying organism. Patients with a higherCD4 count are therefore likely to seek help earlier because they become symptomatic earlier.

It also means that in HIV-infected patients with a “low” CD4 count, NCC lesions detected incidentally on imaging may not present with the expected imaging findings of ringenhancement and oedema. They may present with atypical lesions involving the subarachnoid spaces and the spinal cord, resulting in an imaging dilemma. HIV-infected patients are also susceptible to a number of pathologies,presenting with multiple ring-enhancing lesions of the brain and the spinal cord on imaging.

Intramedullary spinal-cord lesions may be more prevalent in patients with a “low” CD4 count because cell-mediated immunity may play a more important role in preventing haematogenous spread of the parasite to the spinal cord.

Ventricular lesions were found only in patients with a “high” CD4 count (p=0.23). Again, as was the case with racemose lesions, a weakened immune system may have unpredictable effects on the prevalence of extra-axial lesions.

In HIV-infected patients the cysticercosis lifespan may be longer because these patients have a less effective immune-inflammatory response. Also, the immune response in HIV-infected patients declines with the progression of the disease[6].

NCC may be paradoxically worsened by an inflammatory reaction occurring after the initiation of HAART[3]. Three cases, including 1 of our patients, presented with signs and symptoms of probable IRIS. These patients were all from the “high” CD4-count group, but with serial, rather than a singleCD4 count, and the follow-up of the patients’ imaging, as well as clinical presentation, it would be easier to make the diagnosis of IRIS.

There are no reports documenting specific cases with neuro-IRIS associated with NCC, and very few review articles make mention of this specific entity[11,8].However, imaging appearances of NCC in these circumstances would be expected to be classical in nature because of the immune response of the host.

The response rate of cysticidal therapy in HIV patients is 85%, which is similar to the response reported for the general population. However, a lower rate of both complications and symptom presentation may be attributable to a weaker inflammatory response to the dying organisms after the administration of cysticidal drugs or due to the resolution of symptoms produced by specific therapy for CNS infections other than NCC [11].

In our study, 79% from the "high" CD4-count group improved after treatment, whilst 46% from the "low" CD4-count group improved. The CD4count therefore has a prognostic value in these patients.

A limitation of this study is the fact that it is retrospective.The interpretation of the imaging was performed by one radiologist. The imaging interpretation is subjective and therefore subject to inter-observer variation. Despite the small sample size, it constitutes one of the largest case series in the literature.

Conclusion

HIV-infected patients with a"low" CD4 count may demonstrate less ring enhancement, oedema and may more likelypresent with atypical lesions such as subarachnoid and spinal-cord lesions.This may complicate and delay the diagnosis of NCC. We hypothesize that with the initiation of HAART, patients withan increasing CD4 count may present with imaging appearances that are classical in nature.

Legends for figures:

Fig 1 a-c: Spinal-cord neurocysticerci on T1- and T2-weighted MRI.

a: T1-weighted, post-contrast sagittal MRI, demonstrating a thick-rim-enhancing and a smaller, solid enhancing lesion (arrows). The smaller lesion is at the level of T8 and was not seen on the STIR imaging.

b: Sagittal T2 STIR image of the thoracic spine, demonstrating a hyperintense intramedullary lesion at the level of the T8/T9 disc. There is a syrinx extending from the T5/T6 disc to the T10/T11 disc.

c: T1-weighted, post-contrast axial MRI, demonstrating an intramedullary lesion at the level of the T8/T9 disc within the cord.

Fig 1 d-f: Various stages and imaging patterns of neurocysticercosis on T1-weighted gadolinium-enhanced MRI.

d: Thin-rim-enhancing lesions in the cerebellar hemispheres bilaterally (stage 3); thick-rim-enhancing lesions in the right temporal lobe and abutting the floor of the fourth ventricle (stage 2), surrounded by significant oedema.

e: Multiple rim-enhancing lesions of various sizes with minimal surrounding oedema (stage 3); a larger, stage-2 lesion in the left external capsule/claustrum; the lesion in the right frontal lobe demonstrates the characteristic feature of a scolex (stage1).

f: A solid enhancing lesion in the distal medulla and a larger, thick-rim-enhancing lesion impressing on the cerebellar tonsil.

Fig 2 a-c: Axial and Coronal T2-weighted MRI images demonstrating diffuse parenchymal disease.

Parenchymal cysts with significant surrounding odema in the right posterior limb of internal capsule (a and c) as well as diffuse cysts in a parafalcine, centrum semi- ovale distribution. (b)

Fig 2 d-f: Axial and Sagittal T1-weighted gadolinium-enhanced MRI images. Diffuse rim- enhancing cysts in the cerebellar hemispheres (d), grey/ white matter interface of the parietal lobes (e), including a single lesion in the proximal c-spine (black arrow in f).

Fig 3 a-c: Axial post-contrast CT images.

Extensive racemose cysts in bilateral MCA cisterns, ambient cisterns, bilateral Sylvian fissures, sulci of gyrus recti and frontal parafalcine sulci.

Note the mild associated hydrocephalus.

Fig 4 a-c: Axial T2-weighted MRI images.

Large cysts in the anterior horns of the lateral ventricles bilaterally (small black arrow in a). These images also demonstrate large racemose cysts in the Sylvian fissures bilaterally, MCA cisterns, sulci of gyrus recti and left ambient cistern.

Fig 4d: Coronal T2-weighted MRI image.

Large intraventricular cysts (anterior horn of lateral ventricles) as well as racemose cysts in MCA and suprasellar cisterns. There is a giant cyst in the left parieto-temporal lobe which is in continuity with cysts in in the left MCA cistern.

Fig 4e-f: Sagittal and axial T1-weighted MRI images, demonstrating racemose cysts extending along the sylvian fissures and MCA cisterns as well as the left ambient cistern.

Fig 5a-c: Axial T1-weighted, post-contrast images.
Small, conglomerate, rim- enhancing intraparenchymal cysts in right parietal and right occipital lobes with extensive surrounding vasogenic oedema.
There are few, smaller lesions in the left frontal lobe and posterior parafalcine distribution.

Fig 5d-e: Axial T2-weighted MRI images, reveals extensive surrounding vasogenic oedema of lesions in the right occipital and right parietal lobes as well as right basal ganglia.

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Table 1. Imaging features of 13 published cases with NCC and concomitant HIV

Source	MRI or CT	Parenchymal, subarachnoid–cisternal, subarachnoid, ventricular or spinal	Location:	Small (<2cm) Or Giant (>2cm)	Presence of mural nodule (Ca++ or not)	Ring enhance / discoid enhancement	Oedema	Presence of calcified granulomas (inactive)	Other findings	CD4 count Low (<200) High (≥200)
1996 Soto Hernandez (case 1)[7]	CT and MRI	Parenchymal	Right frontoparieto-temporal	Giant	None	No	None	None	None	Low (150 cells/mm^3)
2004 Delobel [8]	CT and MRI	Parenchymal and subarachnoid (brain) as well as spinal (epidural)	2 focal, cortical small lesions (1 in each frontal lobe) Large left temporal lobe cyst (3cm) Lumbar epidural cyst (L3/L4)	Small and giant	None	Ring-enhancement	None	None	Toxoplasma encephalitis	High (241 cells/ $mm^{3)}$
2006 Prasad (case 1)[9]	MRI	Parenchymal	Right parietal, 14mm and multiple others	Small	Enhancing mural nodule right parietal	Ring-enhancement	Significant oedema around right parietal lesion	None	Bacterial brain abscess	High (350 cells/mm^3)
2006 Prasad (case 2) [9]	MRI	Parenchymal	Right temporo-frontal	Small	Enhancing mural nodule in one of temporal lesions	Ring-enhancement	Minimal oedema*	None	Toxoplasma encephalitis	Low (32 cells/mm^3)
2006 Prasad (case 3) [9]	MRI	Parenchymal	Diffuse	Small	Some have enhancing mural nodules	Some with and some without ring-enhancement	Minimal oedema*	None	None	Low (105 cells/mm^3)
2006 Chianura [10]	MRI and CT	Parenchymal, subarachnoid andventricular	Diffuse	Small	None*	Ring-enhancement	Significant oedema	None	None	High (473 cells/mm^3)
2007 Serpa [11]	CT and MRI	Parenchymal	Single, large lesion (4,5x 3x 2 cm) in left	Giant	None	Ring-enhancement	Surrounding oedema	None	None	High (462 cells/mm^3)

			posterior high frontal lobe							
2007 Ramos [12]	CT and MRI	Parenchymal	Large (2,5x 2,8x 2,3 cm) in left temporal lobe and diffuse, small lesions	Small and giant	Enhancing, mural nodules	Ring-enhancement	Significant surrounding oedema	None	None	Low (13 cells/mm^3)
2007 Lattuada [13]	MRI	Parenchymal	Left frontal	Small	Enhancing, mural nodule	Ring-enhancement	Surrounding oedema	None	Toxoplasmosis	High (343 cells/mm^3)
2012 Gupta (paediatric case) [14]	MRI	Starry Sky-parenchymal and subarachnoid	Diffuse parenchymal, subarachnoid and brainstem	Small	Enhancing mural nodules	Focal/discoid enhancement	Extensive oedema	None	Mild, non-communicating hydrocephalus	High (396/mm^3)
2012 Motsepe [15]	MRI	Spinal (Intramedullary and subarachnoid)	T12-L2	Small	No mural nodule	No ring-enhancement	No surrounding oedema	None	Collapse of T12 and fracture of spinous process as result of bony invasion Degeneration of T11- L2	Low (46/mm^3)
2014 Anand (case 1) [16]	CT and MRI	Parenchymal	Bilateral cerebral hemispheres	Small	Ca++ mural nodules	Thin ring-enhancement	Surrounding oedema	Yes	None	High (530/mm^3)
2014 Anand (case 2) [16]	MRI	Parenchymal	Bilateral cerebral hemispheres Single, giant cyst in right parieto-occipital lobe	Small and Ggant	Enhancing, eccentric mural nodules	Mild, ring-enhancement	Significant surrounding oedema	None	None	High (350/mm^3)

* The author made this deduction by looking at the available images in the article.
No comment was made in the article on the presence/absence of oedema

Table 2. Imaging features of 20 of our patients with NCC and concomitant HIV

Source	**MRI or CT**	**Parenchymal, subarachnoid-cisternal, subarachnoid, intraventricular or spinal**	**Location:**	**Small (<2cm) or giant(>2cm)**	**Presence of mural nodule (Ca++ or not)**	**Ringenhance / discoid enhancement**	**Oedema**	**Presence of calcified granulomas (inactive)**	**Other findings**	**CD4 count Low (<200) High (≥200)**
Patient 1	CT and MRI	Parenchymal brain, brainstem and intramedullary spinal lesions	Diffuse parenchymal, brainstem (Pons and medulla) lesions and level of T9	Small	Enhancing mural nodules	Ring-enhancement	Extensive surrounding oedema	None	Syrinx	Low (180 cells/mm^3)
Patient 2	MRI	Parenchymal and subarachnoid (brain) lesions Intramedullary spinal lesion	Diffuse parenchymal and subarachnoid brain lesions and level of C2	Small	None	Ring-enhancement	Extensive surrounding oedema	None	None	Low (118 cells/mm^3)
Patient 3	CT	Subarachnoid-cisternal (Racemose)	Extensive cisternal, Sylvian fissure,anterior hemispheric and frontal sulcal cysts	Small but conglomerate	None	None	None	None	Mild, non-communicating hydrocephalus	Low (74 cells/mm^3)
Patient 4	CT and MRI	,Subarachnoid-cisternal, (racemose) intraventricular	Frontal horns of lateral ventricles, cisterns, left Sylvian fissure and frontal sulci	Small and giant conglomerate	None	No significant ring-enhancement (all extra-axial)	None (all extra axial)	Yes	Non- communicating hydrocephalus	High (559 cells/mm^3)
Patient 5	MRI	Parenchymal and subarachnoid (brain) subarachnoid and intramedullary spine and brainstem lesions	Diffuse parenchymal and subarachnoid brain lesions. Medulla	Small and conglomerate	None	Ring-enhancement	Extensive surrounding oedema	None	Atrophy	High (734 cells/mm^3)

			oblongata and c- spine subarachnoid lesions. Intramedullary T-spine lesions							
Patient 6	CT	Parenchymal and subarachnoid brain lesions	Left parietal lobe	Giant and conglomerate	Eccentric, enhancing mural nodule and others have Ca++ nodules	No significant enhancement	No significant oedema	Yes	Atrophy	Low (180 cells/mm^3)
Patient 7	CT	Parenchymal (brain)	Diffuse and single lesion in brainstem (Pons)	Small	Eccentric, Ca++ and enhancing nodules	Thick, ringenhancement around one lesion	Significant, surrounding oedema around some lesions	None	None	High (460 cells/mm^3)
Patient 8	CT	Subarachnoid (brain)	Single, right frontal lesion	Small	Enhancing mural nodules	Subtle ring enhancement	No oedema	None	None	Low (120 cells/mm^3)
Patient 9	CT	Parenchymal and subarachnoid (brain)	Diffuse	Small	Enhancing mural nodules	Some lesions have ring enhancement, others not	No oedema	Yes	None	High (223 cells/mm^3)
Patient 10	CT	Parenchymal (brain)	Diffuse	Small	None	Ring and discoid enhancement	No oedema	Yes	None	Low (4 cells/ mm^3)
Patient 11	CT	Parenchymal and subarachnoid (brain)	Diffuse	Small	Enhancing and Ca++ mural nodules	Ring enhancement	No oedema	Yes	None	High (477 cells/ mm^3)
Patient 12	CT	Parenchymal and subarachnoid (brain)	Diffuse	Small	Enhancing mural nodules	No significant ring enhancement	No oedema	Yes	None	Low (174 cells/mm^3)
Patient 13	CT	Parenchymal and subarachnoid (brain)	High parietal lobe (small cysts) Single, giant cyst right parieto-occipital lobe	Small and giant	Enhancing mural nodules	No ring enhancement	No oedema	Yes	Non- communicating hydrocephalus	Low (94 cells/mm^3)

Patient 14	CT	Parenchymal, subarachnoid-cisternal (Racemose)	Cysts in MCA cisterns. Giant cyst left temporal lobe	Small and giant	None	Some have mild ring enhancement	No oedema	Yes	Communicating hydrocephalus and TB Meningitis	High (611 cells/mm^3)
Patient 15	CT	Parenchymal, subarachnoid and subarachnoid-cisternal (brain)	Diffuse and within the Sylvian fissures and MCA cisterns. Single brainstem lesion (medulla)	Small	Enhancing and calcified mural nodules	None	No oedema	Yes	None	High (295 cells/mm^3)
Patient 16	CT	Subarachnoid and subarachnoid-cisternal (brain)	Subarachnoid space adjacent to superior sagittal sinus and subarachnoid surface of brain	Small	None	None	No oedema	Yes	None	Low (116 cells/mm^3)
Patient 17	CT and MRI	Parenchymal and subarachnoid (brain)	Diffuse	Small	Enhancing mural nodules	Ring enhancement	No oedema	Yes	Lacunar infarct left corona radiata	Low (98 cells/mm^3)
Patient 18	CT	Parenchymal and subarachnoid (brain)	Diffuse	Small	Enhancing and calcified mural nodules	Discoid and ring enhancement	Surrounding oedema	Yes	Tuberculomas	Low (116 cells/mm^3)
Patient 19	CT	Parenchymal and subarachnoid (brain)	Diffuse	Small	None	None	No oedema	Only calcified granulomas- no cystic lesions	None	High (372 cells/mm^3)
Patient 20	CT and MRI	Parenchymal brain lesions	Two, small intraparenchymal lesions in the left, high parietal lobe	Small	Enhancing mural nodules	Ring enhancement	Extensive surrounding oedema	None	HIV encephalitis	Low (23 cells/mm^3)

Table 3. Comparison of all patients with a low CD4 count (CD4<200) and patients with high CD4 counts (CD4≥200).

Variable (N=33)	**Low CD 4 count (<200 cells/mm^3) N= 17***	**High CD 4 count (≥200 cells/mm^3) N=16***
Imaging modality		
MRIonly	4 (23.5)	5 (31.3)
CT only	8 (47.1)	6 (37.5)
MRI and CT	5 (29.4)	5 (31.3)
Parenchymal / subarachnoid (Brain)		
Parenchymal (brain) only	7 (41.2)	6 (37.5)
Subarachnoid (brain) only	3 (17.6)	1 (6.3)
Parenchymal and subarachnoid	6 (35.3)	9 (56.3)
No parenchymal or subarachnoid (brain)	1(5.09)	0 (0)
Ventricular lesions		
Ventricular lesions	0 (0)	2 (12.5)
No ventricular lesions	17 (100)	14 (87.5)
Rasemose lesions		
Rasemose lesions	1 (5.9)	2 (12.5)
No racemose lesions	16 (94.1)	14 (87.5)
Cisternal lesions		
Cisternal lesions	2 (11.8)	3 (18.8)
No cisternal lesions	15 (88.2)	13 (81.3)
Spinal lesions: sub-characterisation		
Spinal (intramedullary)	2 (11.8)	0 (0)
Spinal (subarachnoid)	0 (0)	0 (0)
Spinal (intramedullary and subarachnoid)	1 (5.9)	1 (6.3)
Spinal (extradural)	0 (0)	1 (6.3)
No spinal	14 (82.4)	14 (87.5)
Spinal lesions		
Spinal only	1 (5.9)	0 (0)
Spinal and others	2 (11.8)	2 (12.5)
No spinal	14 (82.4)	14 (87.5)
Brainstem lesions		
Brainstem lesions	1 (5.9)	4 (25.0)
No brainstem lesions	16 (94.1)	12 (75.0)
Intra- axial or Extra- axial		
Intra- axial only	7 (41.2)	6 (37.5)
Extra- axial only	3 (17.6)	1 (6.3)
Extra- and intra- axial	7 (41.2)	9 (56.3)

Single or Multiple lesions		
Single lesion	2 (11.8)	2 (12.5)
Multiple lesions	15(88.2)	14 (87.5)
Calcified granulomas		
With calcified granulomas	7 (41.2)	7 (43.8)
Without calcified granulomas	10 (58.8)	9 (56.3)
Small and giant		
Small	13 (76.5)	11 (68.8)
Giant	2 (11.8)	1 (6.3)
Small and giant	2 (11.8)	4 (25.0)
Mural nodule		
Mural nodule	11 (64.7)	9 (56.3)
No mural nodule	6 (35.3)	7 (43.8)
Ringenhancement		
Ring enhancement	9 (52.9)	13 (81.3)
No ring enhancement	8 (47.1)	3 (18.8)
Surrounding oedema		
Significant surrounding oedema	5 (29.4)	9 (56.3)
No significant surrounding oedema	12 (70.6)	7 (43.8)
Associations		
Associations	9 (52.9)	7 (43.8)
-Co-infections/abscess	3 (17.6)	3 (18.8)
-Hydrocephalus	2 (11.8)	3 (18.8)
-Infarction	1 (5.9)	1 (6.3)
-Brain atrophy	1 (5.9)	1 (6.3)
-Collapse of spinal vertebrae	1 (5.9)	0 (0)
-Syrinx	1 (5.9)	0 (0)
No associations	8 (47.1)	9 (56.3)
Cysts and calcified granulomas		
Only cystic lesions	10 (58.8)	9 (56.3)
Only calcified granulomas	0 (0)	1 (6.3)
Both cystic and granulomatous lesions	7 (41.2)	6 (37.5)

*Data expressed as N(%)

Table 4. Demographics and clinical presentation of the published cases

Source	Age	Gender	Ethnicity	CD4 count (cells/mm^3)	Clinical presentation
1996 Soto Hernandez [7](Case 1)	29yrs	Male	Latin American	150	Headaches, blurred vision, nausea and vomiting.
2004 Delobel[8]	45yrs	Male	Latin American	241	Right- sided spastic paresis. Brown Sequard syndrome. Left radicular pain and weakness. Cauda equina syndrome.
2006 Prasad[9](case 1)	51yrs	Female	Indian	350	Left- sided seizures.
2006 Prasad[9](case 2)	40yrs	Male	Latin American	32	Left- sided seizures.
2006 Prasad[9]case 3)	72yrs	Male	Latin American	105	Headaches, ataxia and loss of vision.
2006 Chianura[10]	22yrs	Female	Latin American	473	Headache and sensorineural hearing loss.
2007 Serpa[11]	35yrs	Male	Latin American	462	Generalised tonic-clonic seizures. Headaches and right- sided hemiparesis.
2007 Ramos[12]	36yrs	Female	Latin American	13	Headache, nausea and vomiting.
2007 Lattuada[13]	56yrs	Female	African	343	Headache and right- sided seizures.
2012 Gupta[14]	13yrs	Male	Indian	396	Generalised tonic-clonic seizures. Intermittent headaches and vomiting.
2012 Motsepe[15]	46yrs	Female	African	46	Severe pain associated with spasms and weakness of lower limbs. Sensory deficit of light touch, pain and proprioception.
2015 Anand[16](Case 1)	35yrs	Male	Indian	530	Complex, partial seizures with secondary generalization.
2015 Anand[16](Case 2)	40yrs	Male	Indian	350	Complex, partial seizures and sudden loss of left hemifield visual loss of both eyes.

Table 5. Demographics and clinical presentation of our cases

Source	Age	Gender	Ethnicity	CD4 count	Clinical presentation
Patient 1	41yrs	Male	African	180	Weakness and sensory changes in the legs and urinary incontinence. Sensory level T10.
Patient 2	30yrs	Male	African	118	NA
Patient 3	52yrs	Male	African	74	NA
Patient 4	36yrs	Male	African	559	Headaches, double vision, vomiting, photophobia and cerebellar signs.
Patient 5	36yrs	Female	African	734	NA
Patient 6	50yrs	Male	African	180	Generalised tonic-clonic seizures with right- sided weakness and increased tone.
Patient 7	27yrs	Male	African	460	Generalised tonic-clonic seizures.
Patient 8	26yrs	Female	African	120	Seizures.
Patient 9	30yrs	Female	African	139	Seizures.
Patient 10	40yrs	Male	African	57	Focal seizures and weakness of left leg.
Patient 11	31yrs	Male	African	477	NA
Patient 12	53yrs	Male	African	174	Confusion, meningism and generalized seizures.
Patient 13	33yrs	Male	African	94	Confusion, headache and vomiting.
Patient 14	30yrs	Female	African	611	Headache and visual disturbances.
Patient 15	30yrs	Male	African	295	NA
Patient 16	34yrs	Male	African	116	NA
Patient 17	43yrs	Female	African	98	Seizures.
Patient 18	33yrs	Male	African	116	NA
Patient 19	39yrs	Female	African	372	Seizures.
Patient 20	43yrs	Female	African	23	Decreased consciousness and encephalopathy.

Table 6. Comparison of the imaging findings between the published cases and our cases

Variable (n=33)	Published cases (n=13)*	Own cases (n=20)*
Parenchymal/ subarachnoid (Brain)[a]		
Parenchymal (brain) only	9 (69.2)	4 (20.0)
Subarachnoid (brain) only	0 (0)	4 (20.0)
Parenchymal and subarachnoid (brain)	3 (23.1)	12 (60.0)
No parenchymal or subarachnoid	1 (7.7)	0 (0)
Ventricular lesions		
Ventricular lesions	1 (7.7)	1 (5)
No ventricular lesions	12 (92.3)	19 (95.0)
Racemose lesions		
Racemose lesions	0 (0)	3 (15.0)
No racemose lesions	13 (100)	17 (85.0)
Cisternal lesions		
Cisternal lesions	0 (0)	5 (25.0)
No cisternal lesions	13 (100)	15 (75.0)
Spinal lesions		
Spinal lesions	2 (15.4)	3 (15.0)
No spinal lesions	11 (84.6)	17 (85.0)
Spinal lesion: sub-characterisation		
Spinal (intramedullary)	0 (0)	2 (10.0)
Spinal (subarachnoid)	0 (0)	0 (0)
Spinal (intramedullary and subarachnoid)	1 (7.7)	1 (5.0)
Spinal (extradural)	1 (7.7)	0 (0)
No spinal	11 (84.6)	17 (85.0)
Spinal lesions		
Spinal only	1 (7.7)	0 (0)
Spinal and others	1 (7.7)	3 (15.0)
No spinal	11 (84.6)	17 (85.0)
Brainstem lesions		
Brainstem lesions	0 (0)	5 (25.0)
No brainstem lesions	13 (100)	15 (75.0)
Intra- axial or extra-axial[b]		
Intra- axial	9 (69.2)	4 (20.0)
Extra- axial	0 (0)	4 (20.0)
Intra- and extra- axial	4 (30.8)	12 (60.0)
Single or multiple lesions		
Single	3 (23.1)	1 (5.0)
Multiple	10 (76.9)	19 (95)

Calcified granulomas		
With Ca++ granulomas	1 (7.7)	13 (65.0)
Without Ca++ granulomas	12 (92.3)	7 (35.0)
Small and giant		
Small	8 (61.5)	16 (80.0)
Giant	2 (15.4)	1 (5.0)
Small and giant	3 (23.1)	3 (15.0)
Mural nodule		
Mural nodule	8 (61.5)	12 (60.0)
No mural nodule	5 (38.5)	8 (40.0)
Ring enhancement		
Ring enhancement	11 (84.6)	11 (55.0)
No ring enhancement	2 (15.4)	9 (45.0)
Surrounding oedema		
Surrounding oedema	8 (61.5)	6 (30.0)
No oedema	5 (38.5)	14 (70.0)
Associations		
Associations	6 (46.2)	10 (50.0)
No associations	7 (53.8)	10 (50.0)
Cysts and calcifiedgranulomas[c]		
Only cystic lesions	12 (92.3)	7 (35.0)
Only calcified granulomas	0 (0)	1 (5.0)
Both cystic and granulomatous lesions	1 (7.7)	12 (60.0)

*Data expressed as N(%)
[a]p= 0.005
[b]p=0.012
[c]p=0.0019

Table 7. Laboratory findings, treatment and treatment outcomes of the published cases

Source	Laboratory findings	Treatment and outcomes
1996 Soto Hernandez [7] (case 1)		Craniotomy for single, giant cyst. Albendazole HAART and opportunistic infection prophylaxis. Patient became asymptomatic.
2004 Delobel[8]	Positive serum and CSF serology NCC	Lumbar epidural cyst- L3/L4 laminectomy and decompression. Albendazole HAART Empiric Cotrimoxazole Anti-epileptics. Antibiotics Condition improved- able to walk but bladder dysfunction remained. Hemiparesis remained. IRIS a possibility.
2006 Prasad[{9} (case 1)	Toxo- ab positive. Biopsy and culture left frontal lesion: rare abscess. Serum serology positive for NCC	Steroids Albendazole HAART .Empiric Cotrimoxazole Resolution of symptoms
2006 Prasad[1{9} (case 2)	History of Toxoplasmosis. Serum Toxo positive. Serum serology positive for NCC.	Cotrimoxazole, Anti-epileptics HAART No antihelminthic treatment, despite positive serology Patient did well with therapy. Lost to follow- up.
2006 Prasad[{9} (case 3)	Serology positive for NCC.	HAART Dexamethasone Albandazole Symptoms improved.
2006 Chianura[10]	Serology in serum and CSF positive for NCC. Toxo IgG positive. Viral load dropped to undetectable levels but no immune restoration.	Albendazole Dexamethasone Phenytoin HAART 5 years later, CT revealed only calcified granulomas. Favourable outcome, but right-sided hearing loss persisted
2007 Serpa[11]		Aspirated left frontal cyst followed by frontal craniotomy and resection of cyst. HAART Improved without complications IRIS
2007 Ramos[12]	Oral candida Serum serology: positive for NCC Serum serology: negative for Toxo	Albendazole Dexamethasone HAART Empiric treatment with Cotrimoxazole and steroids. Passed away.
2007 Lattuada[13]	Was known with Neurotoxoplasmosis Serum serology: positive for NCC	HAART Mebendazole Dexamethasone Cotrimoxazole Improved on treatment. Discharged in a stable condition Had infection with both NCC and Toxo but was only originally treated for NCC
2012 Gupta[14]	Parents were HIV negative	Midazolam, phenytoin. and valproate Mannitol Albendazole and steroids Acetazolamide Recovered well and was discharged with no neurological deficit.

2012 Motsepe[15]		Cysts were extracted from the subarachnoid space and spinal medulla at T12- L2 and a laminectomy was done at T12 Albendazole Steroids Analgesia Amitryptyline Condition improved. but leg weakness remained unchanged and she could not walk
2015 Anand[16] (case 1)	Serum serology positive for NCC.	HAART No deterioration on treatment.
2015 Anand[16] (case 2)	Serum serology positive for NCC.	HAART Albendazole and steroids At last follow-up, was on Levetiracetam without seizure recurrence.

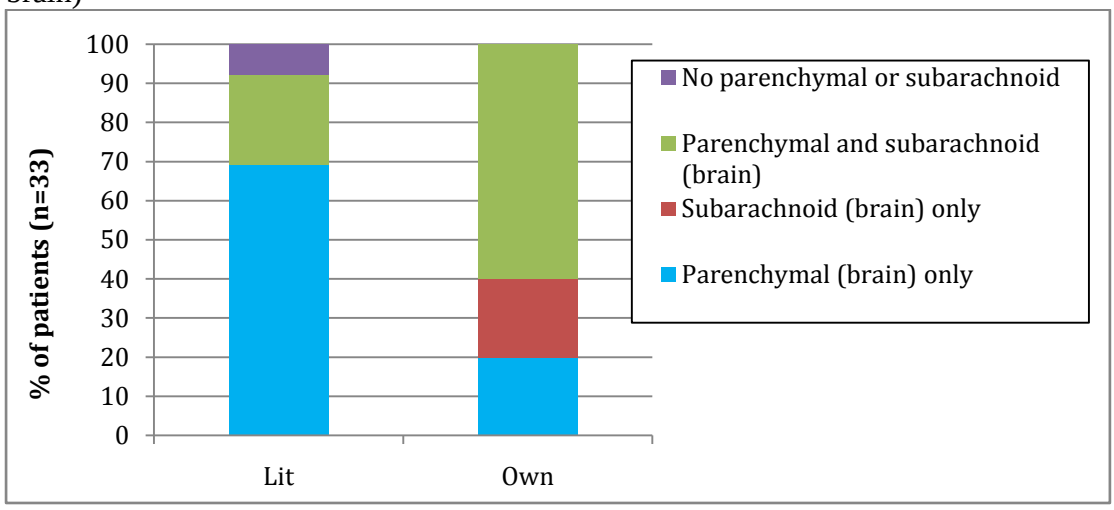
Table 8. Laboratory findings, additional information regarding presentation, treatment and treatment outcomes of our 20 cases

Source	Laboratory findings and additional information regarding presentation	Treatment and outcomes
Patient 1	Indeterminate NCC serum serology	Albendazole and steroids Physiotherapy HAART Was able to walk by means of a walking frame Urinary incontinence improved but continued to have difficulty passing urine. Lost to follow- up Initially treated for ADEM- Treated initially with steroids and TB treatment because of nodular infiltrate on CXR (Before MRI)
Patient 2		NA
Patient 3		NA
Patient 4	Known with NCC Repeated episodes of raised intracranial pressure.	On Praziquantal and steroids. Initially was admitted for ventriculoscopy and cyst removal Epilim HAART Patient was scanned 4x within the following year. The CT scans revealed an overall improvement with marked decrease in the size of the cysts. ?IRIS
Patient 5		NA
Patient 6	Known with a history of epilepsy but defaulted treatment. ? stroke	Praziquantal and Prednisone Epilim Rivotril Condition improved and the patient was discharged.
Patient 7	Admitted for burns	Epilim and Rivotril Albendazole and Decadron Discharged and was to be followed up at burns, HIV and neuro- clinic.
Patient 8	Admitted with history of epilepsy. Defaulted previously started anti-epileptic treatment.	Epilim Albendazole and Prednisone Patient followed up at OPD monthly after discharge. 3 months following discharge, the patient had clinically improved but was not yet on HAART.
Patient 9	NCC was incidentally diagnosed when CT scan was done for staging of high grade NHL of rectum (stage IV). Was on treatment for seizures prior to admission	Albendazole, Prednisone and Carbamazepine HAART was initiated. Patient was started on chemotherapy and is being followed up at the haematology clinic. Follow-up CT done 6 months later showed significant improvement, with calcification of some of the cystic lesions.
Patient 10	NCC serum serology positive. IgM and IgG positive for Toxoplasmosis. Previous TB	Bactrim, Decadron Patient improved and was discharged home.
Patient 11		NA
Patient 12		IV antibiotics (Piperacillin and Tazobactam) Symptoms subsided. Was referred to local clinic for initiation of HAART Follow- up after 2 weeks at Neuro- clinic.
Patient 13	Biopsy confirmed giant NCC cyst	Albendazole, Decadron, Epanutin. Mannitol for raised intracranial pressure.

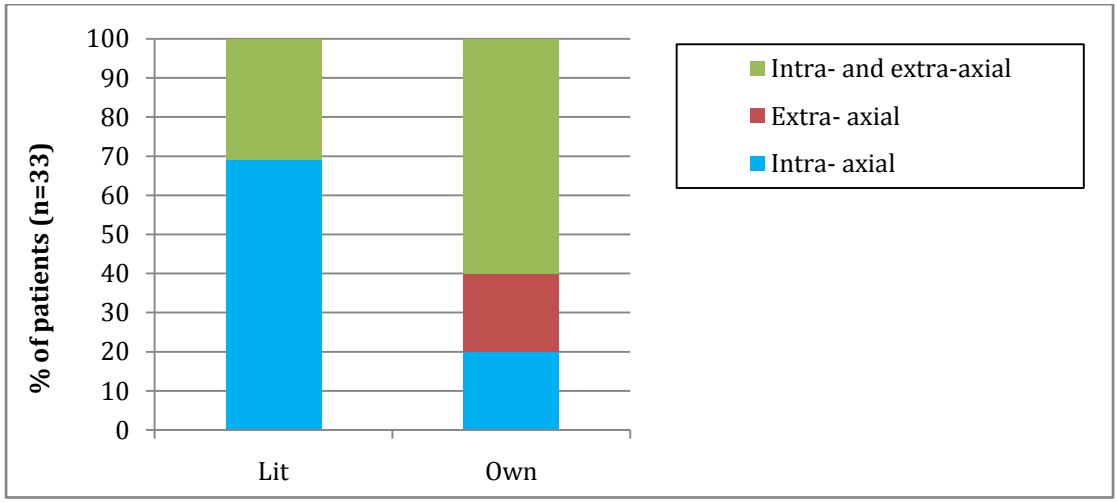
		Was on HAART before admission, but defaulted. HAART was restarted on admission. A month after biopsy was done, CT revealed a significant reduction in size of the giant cyst, with decreased mass effect and no midline shift or hydrocephalus. Was discharged seizure free.
Patient 14	Referred by smaller hospital.	Albendazole, Decadron, Phenytoin VP shunt was inserted and patient was discharged symptom-free.
Patient 15		NA
Patient 16		NA
Patient 17		TB Treatment for TB Meningitis (Dx on LP) Epanutin and Phenytoin Was discharged on HAART, anti- epileptics and TB Rx. Was admitted 3 x in 6months and 3rd CT scan revealed only calcified granulomas. No indication that antiehelminths were given.
Patient 18		NA
Patient 19		CT revealed only calcified granulomas. On HAART and anti- epileptics Followed up at ARV clinic
Patient 20	Toxo- negative	MRI also revealed HIV encephalitis. Started on HAART. Albendazole Patient showed slow improvement. Is still in hospital

*NA= Not available

Graph 1: Published cases vs our cases (parenchymal/subarachnoid location in the brain)



Graph 2: Published cases vs our cases (intra- axial and extra- axial)



Graph 3: Published cases vs our cases (cystic and granulomatous lesions)

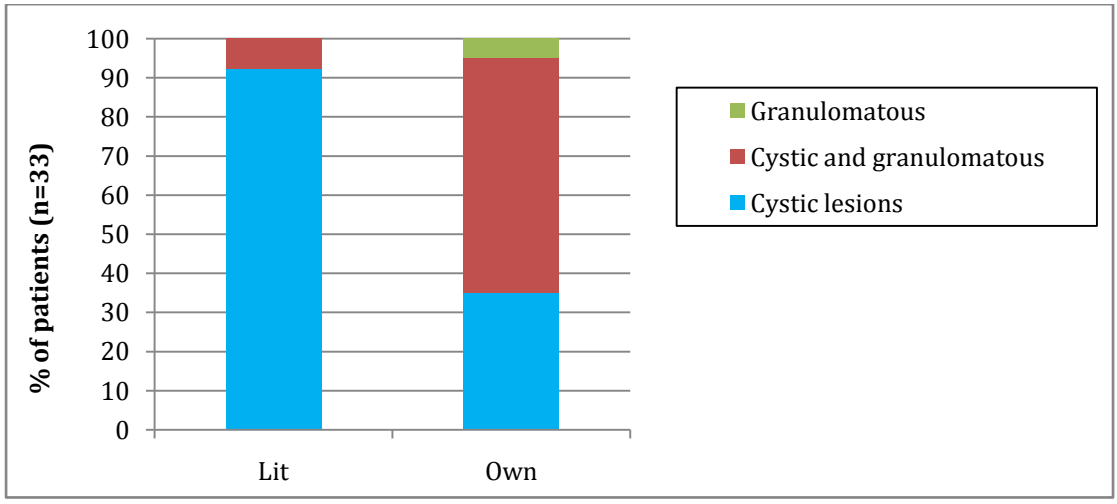


Figure 1 a-c

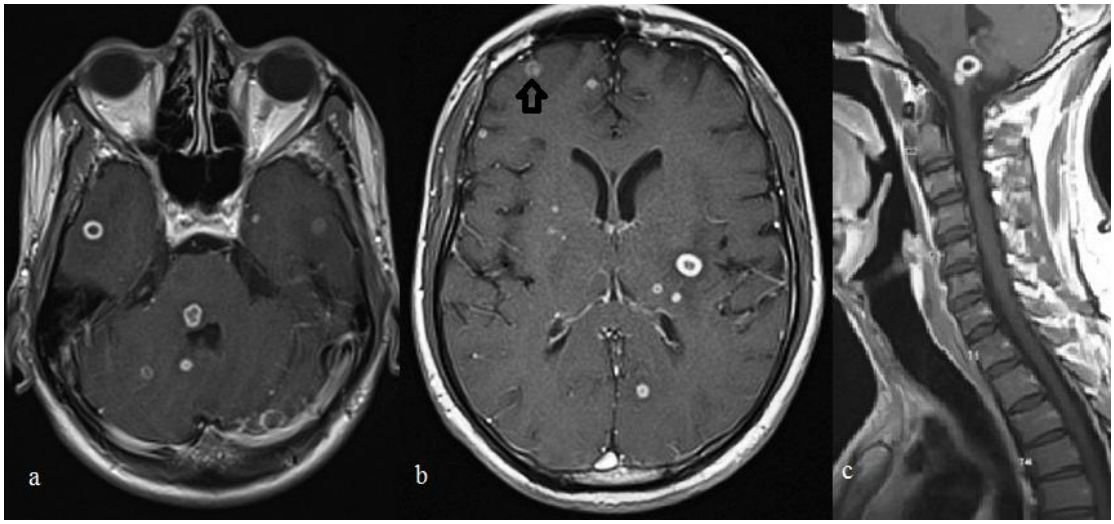


Figure 1d-f

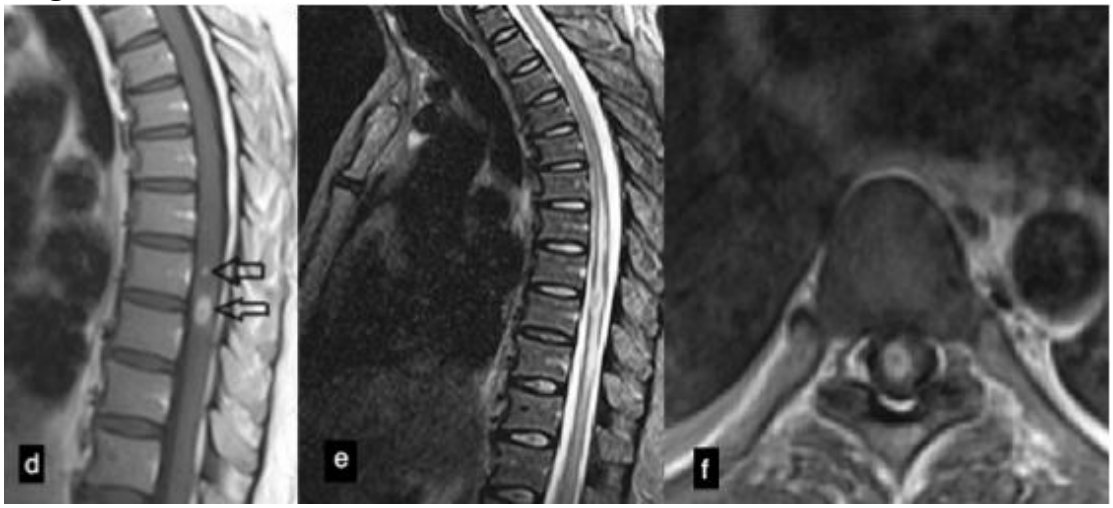


Figure 2a-f

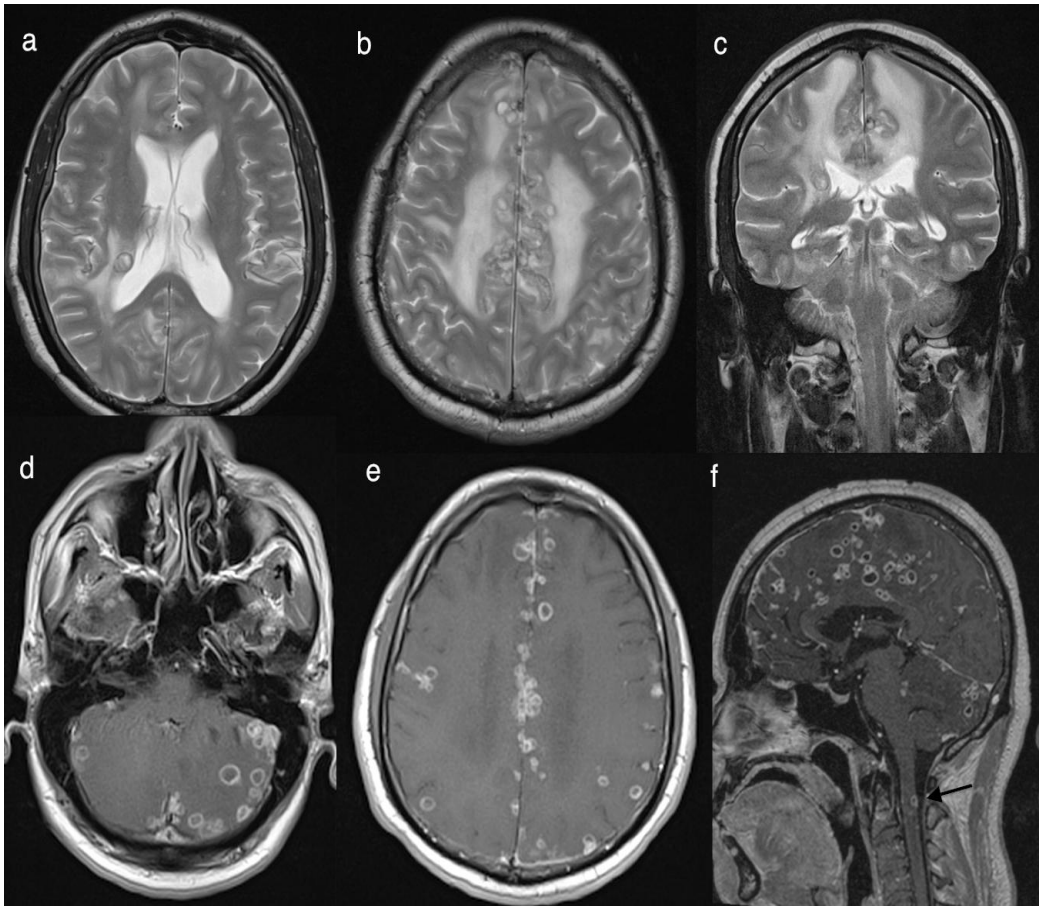


Figure 3a-f

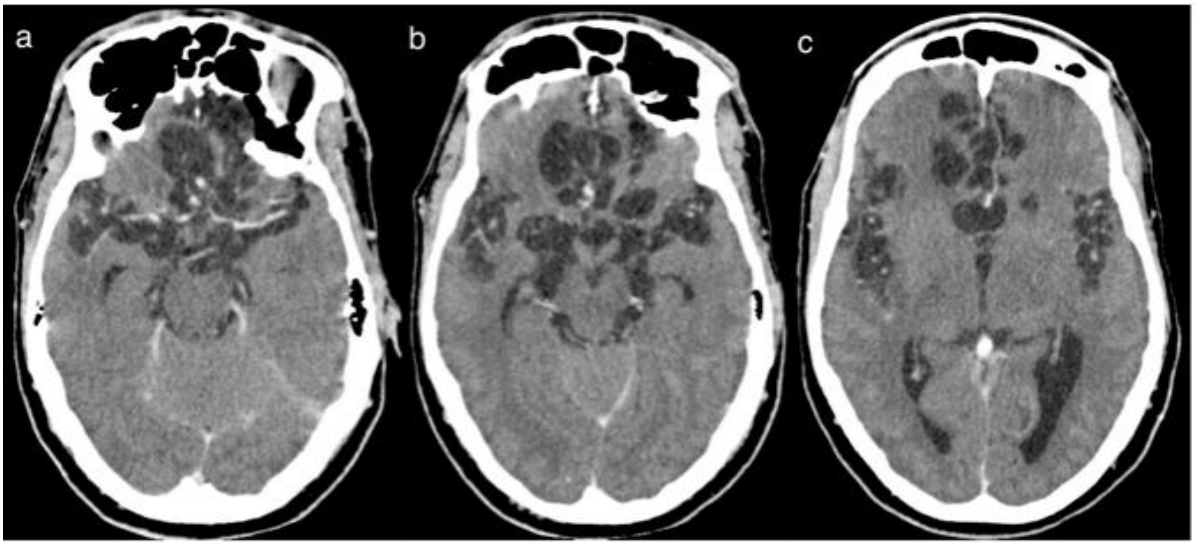


Figure 4a-f

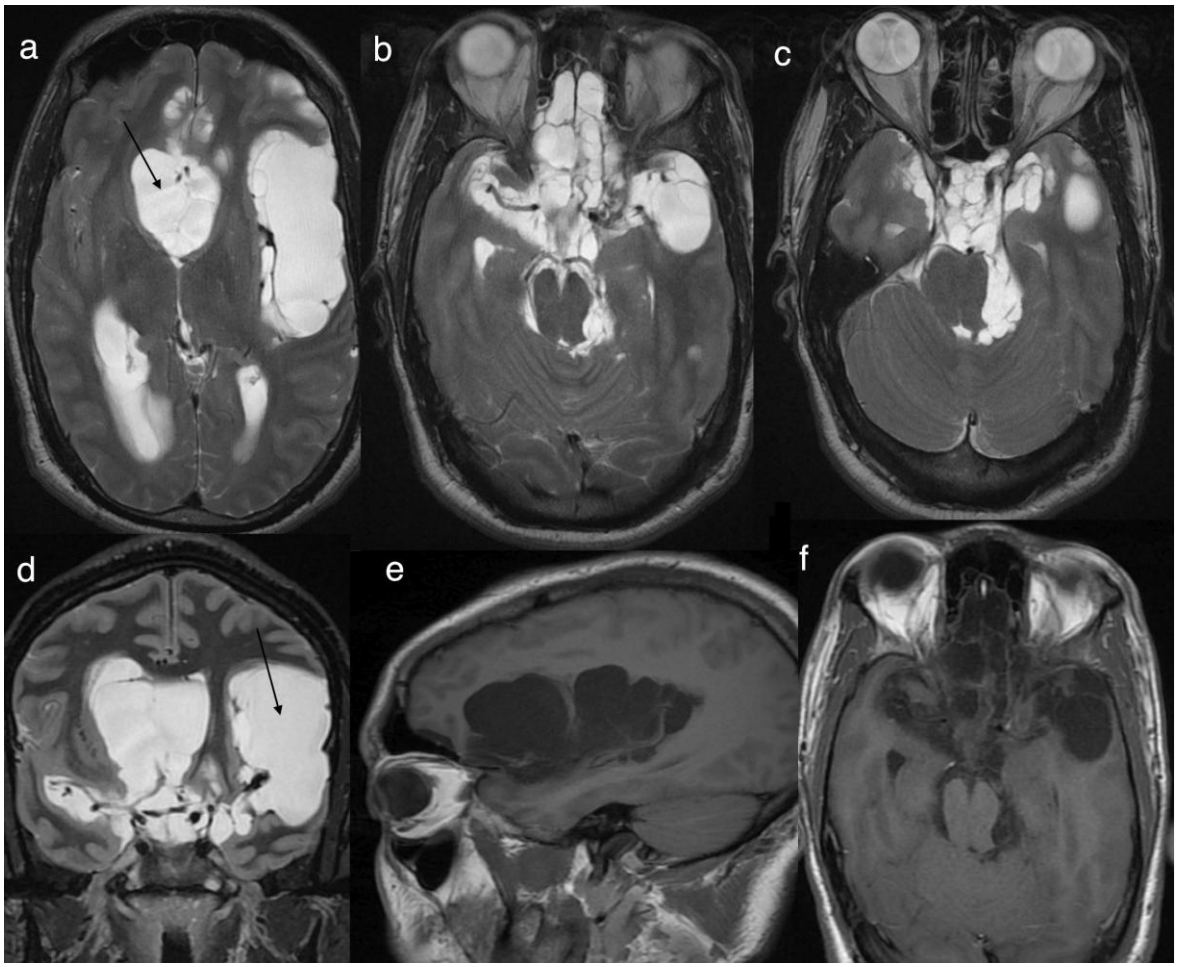


Figure 5a-c

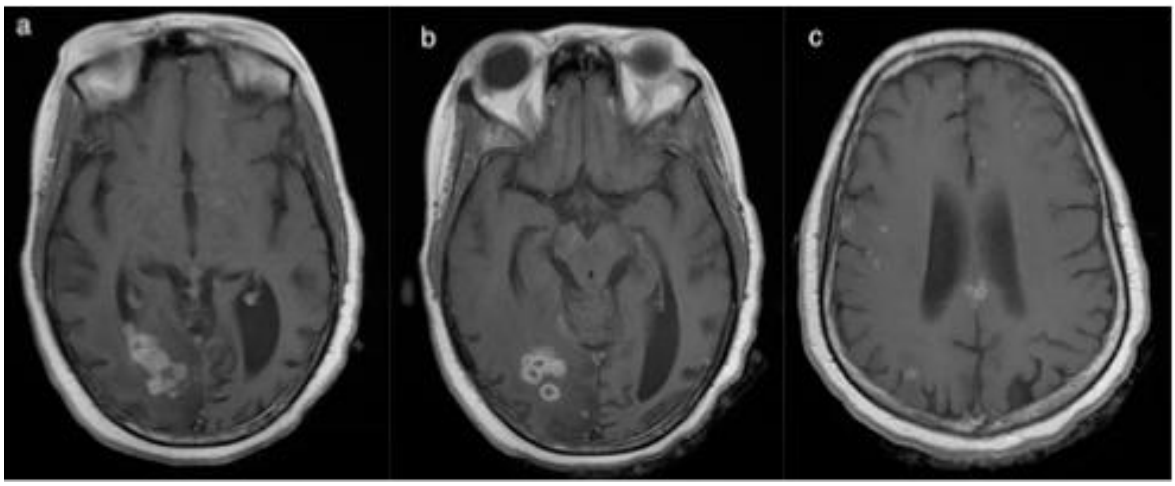


Figure 5d-e