SURGICAL OUTCOMES OF HIV SEROPOSITIVE ADULT PATIENTS WITH INTRACRANIAL HYPERTENSION SECONDARY TO CRYPTOCOCCAL MENINGITIS

By

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As the candidate's supervisor I have approved this thesis for submission.

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Declaration

I, Ndyebo Samkelo Mabovula declare that

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Dedication

This thesis is dedicated to my wife, Dr Phililе Buthelezi, my daughter Liyema and to my parents, Mr Linda Mabovula and Dr Nonceba Mabovula.

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List of abbreviations

ACTA	Advanced Cryptococcal Meningitis Treatment for Africa
AIDS	Acquired immunodeficiency syndrome
AIS	Antibiotic-impregnated shunt
ART	Antiretroviral therapy
C. gattii	Cryptococcus gattii
C. neoformans	Cryptococcus neoformans
CD4+	Cluster of differentiation 4+
Cm	Centimetre
CM	Cryptococcal Meningitis
CMV	Cytomegalovirus
CNS	Central nervous system
CrAg	Cryptococcal antigen
CSF	Cerebrospinal fluid
CT	Computed tomography
DoN	Department of Neurosurgery
ETV	Endoscopic third ventriculostomy
GOS	Glasgow outcome score
H2O	Water
HIV	Human immunodeficiency virus
IALCH	Inkosi Albert Luthuli Central Hospital
IIH	Idiopathic Intracranial hypertension
IQR	Interquartile range
IRIS	Immune reconstitution inflammatory syndrome
KCl	Potassium chloride
KZN	Kwa-Zulu Natal
LMIC	Low-middle-income-countries
LP	Lumbar puncture
LPSI	Lumbar-peritoneal shunt insertion
mEq	Milliequivalent
MRI	Magnetic resonance imaging

MTB	Mycobacterium Tuberculosis
NPH	Normal pressure hydrocephalus
P. jirovecii	Pneumocystis jirovecii
SD	Standard deviation
TBM	Tuberculous meningitis
TNF	Tumour necrosis factor
US	United States
VPSI	Ventriculo-peritoneal shunt insertion
WHO	World Health Organization

Overview of the thesis

The human immunodeficiency virus (HIV) pandemic has resulted in high morbidity and mortality, particularly in Sub-Saharan Africa (1-3). Approximately 36.7 million people worldwide were reported to be living with HIV/AIDS at the end of 2015 (1). The HIV pandemic has affected Sub-Saharan Africa the worst, with over 60% of people infected with HIV living in this region (4, 5). In 2018, approximately 7 700 000 people were reported to be living with HIV in South Africa, with a prevalence rate of 20.4% among the population aged between 15-49 years (2). The Province of KwaZulu-Natal (KZN) has the highest numbers of HIV infections, with a prevalence of 26.8% (6).

Cryptococcal meningitis (CM) is one of the most common opportunistic infections affecting HIV positive patients and is considered an Acquired Immunodeficiency Syndrome (AIDS) defining illness (7-10). Sub-Saharan Africa and Southeast Asia have the highest reported rates of CM at 12-50% and 6-18% respectively (11, 12). In 2014, 223 100 cases of CM were reported globally with HIV-related deaths numbering 181 000 (3).

The World Health Organization (WHO) published guidelines in 2018 on the management of CM in HIV positive patients (8). This was aimed at healthcare providers working in resource limited settings with a high burden of cryptoccocal disease such as South Africa (8). These guidelines emphasised the optimal approach to the diagnosis of CM and prevention through screening of patients with advanced HIV disease by using Cyptococcal Antigen (CrAg) test and treating those who test positive with fluconazole. The guidelines also introduced a shorter one-week antifungal regimen for the induction phase of treatment. Although mentioned as part of recommended drugs, flucytosine is not registered in South Africa.

The Advanced Cryptococcal Meningitis Treatment for Africa (ACTA) trial showed a 10-week reduction in mortality of 24% with a short course of amphotericin B plus flucytosine and a 10-week reduction in mortality of 35% with two weeks of fluconazole and flucytosine when compared to fluconazole monotherapy (13, 14). These results stress the need for the availability of the drug Flucytosine to reduce morbidity and mortality.

In 2019, the Southern African HIV Clinicians Society released updated guidelines for the prevention, diagnosis, and management of cryptococcal disease among HIV-infected persons (15). These guidelines supplemented the WHO 2018 guidelines and were tailored for implementation in resource-limited settings of low-middle-income-countries (LMIC) such as South Africa.

These guidelines included the prevention of CM through screening of patients with advanced HIV disease with a CrAg test and the pre-emptive treatment of patients with CD4+ cell counts below 200cells/µl with fluconazole therapy (15). Advanced HIV disease in adults, adolescents and children above 5 years was defined as a CD4+ cell count of less than 200cells/µl (15). The guidelines also supported the shorter one-week antifungal regimen which has been shown to reduce mortality by 38%.

Intracranial hypertension (or raised intracranial pressure) is a common complication of CM in HIV positive patients and results in high morbidity and mortality if not diagnosed and treated appropriately (7, 15-19). Intracranial hypertension (or raised intracranial pressure) is defined as lumbar puncture opening pressures > 25 cm of water (8, 15, 20). The WHO guidelines recommend a lumbar puncture (LP) for drainage of cerebrospinal fluid (CSF) to maintain opening pressures below 25cm of water or halving the baseline pressure if the opening pressure is extremely high (8). A challenge often faced by low-middle-income countries (LIMC) is the lack of CSF manometers to adequately measure the LP pressures (8). To mitigate this challenge particularly in SA, the use of drip sets has been advocated (15).

Mortality from HIV-associated CM is reported at 10-30% (16) and remains highest in LMIC due to drug-related adverse events, limited availability and high cost of first-line antifungal drugs. Another cause of mortality is immune reconstitution inflammatory syndrome (IRIS) associated with CM and antiretroviral therapy (ART) (21-24).

We conducted a retrospective study of HIV positive adult patients diagnosed with refractory intracranial hypertension (IH) secondary to CM referred for CSF diversion (shunting) to the Department of Neurosurgery (DoN) at Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, between January 2003 and January 2015.

Data collected and analysed included demographics, clinical presentation, CD4+ count, access to anti-retroviral therapy (ART), lumbar puncture (LP) opening pressures, presence or absence of ventriculomegaly (dilated ventricles) on CT brain scans, haematological and clinical biochemistry results. We also evaluated the type of CSF diversion (shunting) procedure performed, intra-operative CSF results and surgical outcomes which included shunt complications and mortality. A comparison was made between the outcomes of Ventriculo-peritoneal shunt insertion (VPSI) and Lumbar-peritoneal shunt insertion (LPSI).

A total of 83 patients were included in this study, 50 (60%) of whom were males. The mean age was 32 ±7.9 years (range 18-52). Headaches [81, 97.5%] and meningism [57, 68%] were the most common clinical features. CSF diversion procedures included VPSI [60, 72%], and LPSI [23, 28%]. Forty-four (53%) patients were on ART, 34 (56.7%) in the VPSI group versus 10 (43.3%) in LPSI group. The mean LP opening pressure was 46.9 ±11.6 cm of water (H2O) in the VPSI group compared to 50.6 ±8.11 cm of H2O in the LPSI group ($p = 0.16$). The median CD4+ count was 76 cells/µl, (Interquartile range (IQR) = 30-129) in the VPSI group compared to 54 cells/µl (IQR = 31-83) in the LPSI group ($p=0.45$).

Shunt complications occurred in 17 (28%) patients in the VPSI group compared to 10 (43.5%) in the LPSI ($p =0.5$). The median CD4+ count in patients who developed shunt complications in the VPSI group was 117 cells/µl (IQR= 76 -129) compared to 48 cells/µl (IQR= 31– 66) in the LPSI group ($p=0.03$). The mean length of hospital stay was 6.2 ±8.5 days (range 2-63) in VPSI and 5.3 ±4.2 days (range 2-23) in LPSI groups ($p= 0.9$). The in-hospital mortality was 15%.

This study showed that patients with a low CD4+ cell count had an increased rate of shunt complications. LPSI were associated with a higher rate of shunt complications especially in those with low CD4+ cell counts. In a country with high burden of HIV/AIDS, CSF diversion is still an important option for treating refractory intracranial hypertension secondary to HIV associated CM. Access to ART, prevention, early diagnosis and treatment of CM are vital in the prevention of complications to related to this infectious disease.

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Part 1: The Review of Literature

1. Introduction

There were approximately 36.7 million people worldwide living with HIV/AIDS at the end of 2015, of these, 1.8 million were children aged less than 15 years old (1). The HIV pandemic has been most severe in Sub-Saharan Africa with over 60% of people diagnosed with HIV/AIDS living in this region (7, 8, 11, 12, 25). In 2018, there were 7 700 000 people living with HIV infection in South Africa with a prevalence rate of 20.4% among the population group aged between 15-49 years (2). The province of KZN has the highest infection rate in South Africa reported at 26.8%(6).

Cryptococcal Meningitis (CM) is a common condition, affecting majority of HIV positive adult patients and is associated with increased morbidity and mortality (7, 26-30). The highest rates of CM have been reported in the HIV positive population from Sub-Saharan Africa (4, 5, 31).

CM is caused by infection with the encapsulated yeast called Cryptococcus neoformans (C. neoformans) and is an AIDS-defining illness in patients with late-stage HIV infection, particularly in Southeast Asia, Southern and East Africa (7-12).

Cryptococcosis represents a major life-threatening fungal infection in HIV positive patients, however, it may also affect HIV negative patients, as a complication of organ transplantation, reticuloendothelial malignancy, corticosteroid treatment, or sarcoidosis due to suppressed immunity.

Intracranial hypertension (or raised intracranial pressure) is a common complication of CM in patients diagnosed with HIV/AIDS and requires prompt diagnosis and management in order to reduce associated morbidity and mortality (7, 15-19). The role of a Neurosurgeon in the management of CM is defined by shunting of CSF either by ventriculo or lumbar-peritoneal shunt insertion as the last resort to control refractory intracranial hypertension following failure of medical therapy and intermittent lumbar punctures.

2. Epidemiology of Cryptococcal meningitis

In the United States (US), the annual incidence of cryptococcosis among HIV-infected patients is reported at 1.8–6.7 cases per 100,000 with up to 89% diagnosed in the central nervous system (CNS) (32). CM is the fourth most common opportunistic infection after Pneumocystis jirovecii (P. jirocecii), cytomegalovirus (CMV) and mycobacterium tuberculosis (MTB) in HIV positive patients. The CNS manifestations of cryptococcosis account for up to 66-89% of solid organ involvement and are far more common than pulmonary, gastrointestinal and cutaneous manifestations. The prevalence of cryptococcal antigenaemia is reported at 2.9% in HIV-infected patients with CD4+ counts of <100 cells/μL and 4.3% in those with CD4+ counts <50 cells/μL (18).

Worldwide, approximately 1 million cases of HIV-associated CM occur annually and the disease accounts for more than 600 000 deaths annually (33). In High Income countries, the widespread use of antiretroviral therapy (ART) has lowered the incidence of cryptococcosis, however, the incidence and mortality from the disease remain extremely high in areas with uncontrolled HIV disease due to limited healthcare resources and access to ART (33).

In Southeast Asia and Africa, cryptococcosis is a common AIDS-related infection when compared to Europe and North America. In Thailand, cryptococcosis accounted for 19% of AIDS-defining illnesses between 1994 and 1998 (12). In Uganda, the incidence of cryptococcal disease in patients with CD4 counts <200 cells/μL was estimated at 10.3 cases per 100 000 (34).

In the Gauteng province, South Africa, the incidence of cryptococcal meningitis was reported to be 18.1 per 100 000 cases (35). Over a 4-year period between 2009-2012, cryptococcal meningitis was more common than tuberculous meningitis and pneumococcal meningitis among HIV-infected individuals in the Gauteng province (35).

3. Cryptococcal Meningitis in Kwa-Zulu Natal

The prevalence of CM in KZN is currently not reported according to our knowledge. Moosa et al conducted a study of 44 HIV-positive patients in Durban, South Africa, where they found that CM was an AIDS-defining illness in 84% of the study cohort (9). They reported a mortality rate of 64% despite appropriate antifungal therapy with amphotericin B and fluconazole. A prospective study of 186 patients by Lightowler et al showed a 28% mortality at 14 days and 32.3% mortality by day 28 in patients with CM despite being on antifungal therapy (36). There are currently no studies reporting on the surgical outcomes, namely CSF diversion (shunting) procedures in HIV positive patients diagnosed with refractory intracranial hypertension secondary to CM in the province of KZN, which has a high burden of HIV infections.

4. Pathophysiology of Cryptococcal Meningitis

Cryptococcus is a genus of basidiomycetous fungi with more than 30 species commonly found in the environment (37). The most common species causing clinical disease in humans are Cryptococcus neoformans (C. neoformans) and Cryptococcus gattii (C.gattii). C. neoformans is found globally in soil, excretions of pigeons and environmental scavengers such as amoeba and sow bugs.

Cryptococcosis occurs primarily by inhalation of the infectious fungi and deposition into pulmonary alveoli. Primary pulmonary infection may be initially asymptomatic. The host immune response leads to deposition of alveolar macrophages, helper T-cells, tumour necrosis factor (TNF), interferon-$_{\gamma}$, and interleukin-2 resulting in granulomatous inflammation (37).

Following the suppression of host immunity, the yeast can grow and disseminate outside pulmonary lymph node complexes. Dissemination to the CNS occurs through haematogenous spread within phagocytes or as yeast cells. Invasion of the blood-brain barrier occurs via transcytosis or free yeast forms leading to fungal seeding in the CNS (37).

Symptoms usually develop over a period of several weeks due to a progressive accumulation of fungal organisms in the CNS. Meningoencephalitis occurs as a result of fungal seeding in the subarachnoid space, and brain parenchymal involvement with or without cryptococcoma formation and results in intracranial hypertension and cranial neuropathies.

Common clinical presentations include: (i) headache (ii) confusion (iii) lethargy (iv) obtundation (v) coma (vi) nausea (vii) vomiting (viii) visual disturbances (ix) fever (x) neck stiffness (xi) hearing defects (xii) seizures (xiii) gait abnormalities and (xiv) choreoathetoid movements.

5. Pathophysiology of intracranial hypertension

Normal intracranial pressure in adults ranges between 7-15mmHg. Intracranial hypertension or raised intracranial pressure is diagnosed when LP opening pressures are ≥25cm of water (H20) (38). Intracranial hypertension occurs in up to 75% of patients with CM and remains a significant cause of morbidity (15). The symptoms of CM can be subacute or chronic in nature and are commonly associated with intracranial hypertension (raised intracranial pressure). Intracranial hypertension may present as severe headaches, vomiting, confusion, depressed level of consciousness, cranial nerve palsies or visual loss.

Graybill et al in a study of 221 patients reported that 27% had LP opening pressures of more than 25cm of H2O on initial LP (39). Several mechanisms have been postulated in the development of intracranial hypertension in CM. These include; obstruction of outflow of CSF by blockage of the arachnoid villi, fungal polysaccharide aggregation in the arachnoid villi and subarachnoid spaces (40). Refractory intracranial hypertension is defined as a sustained raised intracranial pressure greater than 25cm of H2O despite adequate medical therapy and daily LPs for more than 1 week (8).

6. Diagnosis of Cryptococcal Meningitis

Computed tomography (CT) or magnetic resonance imaging (MRI) scan should be done prior to performing a lumbar puncture in patients presenting with focal neurological deficits or a history of slowly progressive meningitis to rule out space occupying intracranial lesions.

The Southern African HIV Clinicians Society recommends that all HIV-seropositive adults and adolescents with clinically suspected meningitis or a positive blood CrAg should be investigated for cryptococcal antigenaemia. This is performed when blood samples of HIV positive patients are found to have a CD4+ cell count below 200cells/µl. The samples are then sent for reflex CrAg testing and patients who test positive are pre-emptively treated as per the guidelines (7, 8, 15). CSF sampling for India ink smear, fungal culture and cryptococcal latex agglutination test is performed for confirmatory diagnosis when the patient displays neurological symptoms.

This screening is necessary as a period of 4 weeks of antifungal therapy is required prior to the initiation of ART due to adverse effects of IRIS.

7. Neuro-radiological features of Cryptococcal meningitis

Studies have demonstrated that despite elevated LP opening pressures, the majority of patients do not demonstrate ventriculomegaly/ dilated ventricles on CT/ MRI brain scans (41). The mechanism for this is not clear, but some authors have postulated that cryptococcal capsular polysaccharides coating the surfaces of the brain, as well as within the ependymal tissue, lead to failure of the ventricles to dilate following increase in the volume of CSF.

A neuro-radiology based study of 30 patients by Khan et al reported cryptococcomas (10%), normal CT brain scans (13.3%), hydrocephalus (16.7%), gelatinous pseudocysts (23.3%) and dilated Virchow-Robin spaces (26.7%) (42). The mean CD4 count was 44 cells/µl and overall mortality was 31%.

8. Treatment of Cryptococcal Meningitis

8.1 **Medical Treatment**

CM is treated medically as per the WHO and Southern African HIV Clinicians guidelines (8, 15). This includes; 2-week induction, 8-week consolidation and 12-month maintenance phases.

8.1.1 **Induction phase**

The induction phase of treatment includes 1 week of amphotericin B deoxycholate (1mg/kg/day) and flucytosine (100mg/kg/day in 4 divided doses). This is followed by 1 week of fluconazole (1200mg daily). Alternative options include 2 weeks of fluconazole (1200mg daily) and flucytosine (100mg/kg/day in 4 divided doses).

If flucytosine is unavailable, patients are initiated on 2 weeks of amphotericin B deoxycholate (1mg/kg/day) and fluconazole (1200mg daily). In patients with renal dysfunction, 1 week of liposomal amphotericin B (3mg/kg/day) and flucytosine (100mg/kg/day in 4 divided doses). This is followed by 1 week of fluconazole.

8.1.2 **Consolidation phase**
The 8-week consolidation phase of treatment includes fluconazole 800mg daily.

8.1.3 **Maintenance phase**
The maintenance phase of treatment is continued for at least 12 months until patient's CD4+ cell count is above 200 cells/µl and the HIV viral load is suppressed. Patients are maintained on fluconazole 200mg daily.

8.2 **Adverse effects of antifungal therapy**
Adverse effects of antifungal therapy are related to drug toxicities following the initiation of amphotericin B. Common adverse effects include hypokalemia, nephrotoxicity and anaemia. The following recommendations are made: (i) Twice-weekly monitoring of potassium, magnesium and creatinine, (ii) Weekly monitoring of haemoglobin, (iii) Pre-hydration with normal saline and electrolyte replacement before each Amphotericin B infusion (8, 15).

8.2.1 **Pre-hydration protocol**
Administration of one litre of Normal Saline fluid with 20mEq of Potassium chloride (KCl) over two hours before each controlled infusion of Amphotericin B and one to two 8mEq KCl tablets orally twice daily. An additional 8mEq KCl tablet twice daily may be added during the second week. If available, magnesium supplementation should be provided (two 250mg tablets of magnesium trisilicate or glycerophosphate twice daily, or magnesium chloride 4mEq twice daily) (8, 15).

8.3 **Lumbar puncture**
Intracranial hypertension among these patients remains a problem necessitating daily LPs to control the CSF pressures, as this is critical to patient survival. Failure to control elevated CSF pressure may result in blindness, permanent neurologic deficits, or death (17-19, 43).

The Southern African HIV Clinicians Society recommended an LP to measure the baseline opening pressures with the use of a manometer. If opening pressures are recorded above 25cm of H2O, removal of 10 to 30ml of CSF was recommended in order to control the pressures. For patients with extremely high LP opening pressures, drainage of CSF to pressures 50% that of baseline was recommended (15).

Repeat LP was also recommended in patients with refractory intracranial hypertension especially if they remain symptomatic. Daily LPs may be necessary in some patients to control intracranial

hypertension; however, some may not be able to tolerate repeat daily LPs (15, 19). Referral to a Neurosurgeon for shunting of CSF is considered in those patients who fail to respond to daily LPs for more than 1 week (15).

8.4 **Lumbar drain insertion**

Lumbar drains are suitable therapeutic options for patients with intracranial hypertension with or without ventriculomegaly. They have been shown to significantly reduce elevated CSF pressures through continuous drainage of CSF (44). Advantage of lumbar drainage is avoidance of permanent CSF shunting and repeat lumbar punctures. Lumbar drains are recommended for a period of 3-5 days (44).

The disadvantages of lumbar drains are related to over drainage of CSF (3-7% of cases), tentorial and tonsillar herniation (44). These complications are common in patients who require prolonged drainage of CSF in order to achieve baseline pressures of 50% of initial opening pressure. Further complications include subdural haematoma and chronic CSF leak (45).

9. Ventriculoperitoneal Shunt insertion in HIV positive patients

The ventriculo-peritoneal shunt (VPS) infection rate in HIV positive patients is unacceptably high (46, 47). The overall VPS infection rate in HIV negative patients is reported at 1-5%, when compared to HIV positive patients, where it is reported at 5-15% (47). Low CD4+ count level is a major risk factor of VPS infection in HIV positive patients (46-49).

Tuberculous meningitis (TBM) is a common cause of hydrocephalus in patients with advanced HIV disease especially in LMIC (46, 48-50). Poor outcomes have been reported in patients with TBM and low CD4+ count (46, 48, 50). Shunt complication rates in this group of patients have been reported at 13.5- 32.3% (51).

10. Lumbar peritoneal shunt insertion in HIV positive patients

Lumbar peritoneal shunts (LPSs) have been shown to be effective in treating both hydrocephalus and non-hydrocephalus conditions presenting with raised intracranial pressure (52). Apart from its use in patients with chronically raised intracranial pressures such as CM, LPSs are used in various other conditions which include Idiopathic intracranial hypertension (IIH), Normal pressure hydrocephalus (NPH), CSF leaks and pseudomeningoceles (52).

Common complications of LPSs include shunt obstruction (4-14%), CSF leak, over drainage (1-15%), shunt migration, tension pneumocephalus and subdural haematomas. LPSI infection rates vary from 1-9% with shunt revision rates ranging from 11-50% (52).

11. Microbiology of shunt infection in HIV positive patients

Staphylococcus species are by far the most common organism (up to 90%) responsible for shunt infections (44, 47, 52, 53). Antibiotic-impregnated shunts (AIS) have been shown to be effective in reducing shunt infection rate (53). A study performed by Govender et al in Durban, KZN evaluated the efficacy of AIS in reducing shunt infection when compared to non-AIS. They found a 5% infection rate in patients in whom an AIS was inserted compared to a 13.3% in those undergoing non-AIS (53).

12. Morbidity and Mortality

Mortality from HIV-associated CM is reported at 10-30% (16). Mortality remains highest in LMIC. This is due to the limited availability and high cost of first-line antifungal drugs, drug-related adverse events and complications of raised intracranial pressure. Immune reconstitution inflammatory syndrome following initiation of ART is another significant cause of mortality (21-24).

A study by Cherian et al identified 50 patients with CM, 13 (26%) were treated with VP shunts, 16 (32%) treated with serial LP and 21 (42%) were treated with medical therapy only. A mortality of 15% (n= 2/13) was reported in the group treated with VPS compared to 22% (n= 8/37) mortality in those treated with medical therapy and serial LPs alone (19). Graybill et al in a study of 381 patients with HIV associated CM reported a mortality rate of 9.5% (39).

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Part 2: A submission ready manuscript.

Surgical outcomes of HIV seropositive adult patients with intracranial hypertension secondary to cryptococcal meningitis.

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Abstract

Background

Cryptococcal meningitis (CM) is common in the HIV-infected population and is associated with increased morbidity and mortality largely due to intracranial hypertension (IH). The purpose of this study was to report on the surgical outcomes of cerebrospinal fluid (CSF) shunting in HIV-positive adult patients diagnosed with refractory IH secondary to CM.

Materials and methods

Retrospective study which included all HIV-positive adults diagnosed with refractory IH secondary to CM shunted between January 2003 and January 2015. Data collected and analysed included demographics, clinical presentation, access to anti-retroviral therapy (ART), Lumbar puncture (LP) opening pressures, CD4+ count, type of CSF shunting procedure, CSF, haematological and biochemical results. A comparison was made between the outcomes of Ventriculo-peritoneal shunt insertion (VPSI) and Lumbar-peritoneal shunt insertion (LPSI).

Results

A total of 83 patients were included in this study, 50 (60%) of whom were males. The mean age was 32 ±7.9 years (range 18-52). Headaches [81, 97.5%] and meningism [57, 68%] were the most common clinical features. CSF diversion procedures included VPSI [60, 72%], and (LPSI) [23, 28%]. Forty-four (53%) patients were on ART, 34 (56.7%) in the VPSI group versus 10 (43.3%) in LPSI group. The mean LP opening pressure was 46.9 ±11.6 cm of water (H20) (range 14-65) in the VPSI group compared to 50.6 ±8.11 cm of H20 (range 30-65) in the LPSI group (p = 0.16). The median CD4+ count was 76 cells/µl, Interquartile range (IQR= 30-129) in the VPSI group compared to 54 cells/µl (IQR= 31-83) in the LPSI group (p=0.45).

Shunt complications occurred in 17 (28%) patients in the VPSI group compared to 10 (43.5%) in the LPSI (p =0.5) group. The median CD4+ count in patients who developed shunt complications in the VPSI group was 117cells/µl (IQR= 76-129) compared to 48cells/µl (IQR= 31– 66) in the LPSI group (p=0.03). The mean length of hospital stay was 6.2 ±8.5 days (range 2-63) in VPSI and 5.3 ±4.2 days (range 2-23) in LPSI groups (p= 0.9). The in-hospital mortality was 15%.

Conclusion

This study showed that patients with a low CD4+ cell count had an increased rate of shunt complications. LPSI were associated with a higher rate of shunt complication especially in those with low CD4+ cell counts. In a country with high burden of HIV/AIDS, CSF diversion is still an important option for treating refractory intracranial hypertension secondary to HIV associated CM. Access to ART, prevention, early diagnosis and treatment of CM are vital in the prevention of complications to related to this infectious disease.

Keywords: HIV, Meningitis, Intracranial hypertension, Shunt, Amphotericin B

Introduction

The Human Immunodeficiency Virus (HIV) pandemic has overburdened an already strained public health service in South Africa, with wide-ranging social and economic ramifications (1). As of 2018, South Africa had 7 700 000 HIV infections and a prevalence rate of 20.4% among the population aged between 15-49 years (1). The Province of KwaZulu-Natal (KZN) has been the most severely affected, with the highest nation-wide prevalence rate at 26.8% (2).

The HIV pandemic ushered an era in which illnesses that were previously considered rarities have become daily occurrences. Cryptococcal meningitis (CM), an AIDS-defining illness in patients with late stage infection has become one of the most common opportunistic infections affecting HIV positive patients. Countries in Sub-Saharan Africa and Southeast Asia reported annual prevalence rates of CM at 12-50% and 6-18% respectively (3-8).

Intracranial Hypertension (or raised intracranial pressure) is a common complication among these patients and results in high morbidity and mortality if not recognized and treated early (5, 9-13). Despite optimal medical therapy, a subset of these patients develop refractory intracranial hypertension, which may require permanent CSF diversion procedures (9, 13-17).

Currently there is no consensus as to the best form of CSF shunting procedure in this cohort of patients. Selecting the most suitable candidates for surgery while preventing shunt complications is vital in this group of patients due to their underlying immunocompromised status. The purpose of this study was to report on the surgical outcomes of CSF shunting in HIV-positive adult patients diagnosed with refractory intracranial hypertension secondary to CM. We compared outcomes between ventriculo-peritoneal insertion (VPSI) and lumbar-peritoneal shunt insertion (LPSI) in this cohort of patients.

Materials and methods

We conducted a retrospective chart review of all HIV positive adult patients (≥ 18 years) with a diagnosis of refractory intracranial hypertension secondary to CM referred for permanent CSF diversion to the Department of Neurosurgery (DoN) at IALCH in Durban, KZN. The study period was between January 2003 and January 2015.

Data collected and analysed included demographics, clinical presentations, HIV associated co-morbidities, CD4+ count levels, lumbar puncture (LP) opening pressures, access to ART, presence or absence of ventriculomegaly/ dilated ventricles on CT or MRI brain scans, haematological and biochemical results. We also evaluated the type of CSF diversion procedure performed and intra-operative CSF results. A comparison was made between the outcomes of ventriculo-peritoneal shunt insertion (VPSI) and lumbar-peritoneal shunt insertion (LPSI) in terms of shunt survival, shunt complications, length of hospital stay, and mortality. We also further analysed whether CD4+ count levels, and lack of access to ART were associated with shunt sepsis. Follow-up included outpatient consultations and telephonic interviews of patients or their relatives.

The exclusion criteria were HIV negative patients with CM, those less than 18 years of age and incomplete medical records. Ethical approval was granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Ref No: BE060/18).

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics of patients. Frequency distribution of numeric data was examined for normality and means or medians.

Categorical factors such as gender was identified using Chi square tests. Numeric data such as age, LP opening pressures, CD4 count, CSF, haematological and biochemical results were compared using T-test or Wilcoxon tests.

Significant factors at the bi variate level were included in a logistic regression model to identify individual risk factor association with shunt complications. Kaplan-Meir graph and log-rank test was used to assess shunt survival analysis and length of hospital stay in the VPSI and LPSI groups. Data was analysed using Stata v13 and a p value of <0.05 was considered statistically significant.

Results

Patient demographics

A total of 1382 patients diagnosed with HIV were treated in the DoN during the study period, of which 83 (6%) were referred for permanent CSF diversion after a diagnosis of refractory IH secondary to CM. Majority were males [50, 60%], while the rest were females [33, 40%]. The mean age was 32 ±7.9 years (range 18-52).

The most common clinical presentations were headaches (n= 81; 97.5%), meningism (n =57; 68%), vomiting (n= 52; 62.5%) and altered mental status (n=47; 54%) (Figure 1). Thirteen (16%) patients were found to have HIV associated co-morbidities such as pulmonary tuberculosis (PTB) [n=12, 14.4%] and molluscum contagiosum [n=1, 1,2%]. CT brain scans revealed ventriculomegaly/dilated ventricles in 68 (82%) patients, while in 15 (18%) patients the ventricles were normal size (Figure 2). Neuro-radiology imaging further revealed that 10 (12%) patients had associated inflammatory intracranial mass lesions, while two (2.4%) had infarcts (Figure 3). Forty-four (53%) patients were on ART, 34 (56.7%) in the VPSI group and 10 (43.3%) in LPSI group. The overall mean CD4 count was 108cells/µl ±11.7cells/µl (range 28-138). Eight patients (10%) had CD4 count above 200cells/µl, while the rest 75 (90%) had CD4 count less than 200cells/µl.

Comparison of the demographics, LP opening pressures, CD4 count, CT brain, haematological, biochemical and CSF results of the VPSI and LPSI groups are shown in table 1.

Surgical Management

The CSF diversion procedures performed were VPSI (n= 60; 72%) and LPSI (n =23; 28%) (Table 1). Thirty-seven (62%) antibiotic impregnated shunts (AIS) and 14 (23%) non-antibiotic impregnated shunts (NAIS) were used in in VPSI group, while in nine (15%) patients the type of shunt used was not documented. All LP shunts were non-antibiotic impregnated. VPSI (n=55/60, 91.7%) was the surgical procedure of choice in majority of patients with ventriculomegaly/ dilated ventricles compared to LPSI (n=13/23, 56.5%) (p=<0.001) (Table 1).

Shunt survival

A comparison of the shunt survival in the VPSI group versus LPSI group is shown in figure 4. The demographic and laboratory data of HIV positive patients who developed shunt complications in the VPSI and LPSI groups are shown in Table 2. Overall shunt complications occurred in 27 (31%) patients, 17 (28%) in the VPSI group and 10 (43.5%) in LPSI group. Mechanical shunt obstruction occurred in nine (52%) patients in the VPSI, compared to two (20%) in the LPSI. Septic shunts complications occurred in eight (48%) patients in the VPSI group compared to eight (80%) in the LPSI insertion group. The most common isolated organisms were *staphylococcus epidermidis* (n=12/16, 75%) and *staphylococcus aureus* (n=4/16, 25%).

More females developed shunt sepsis compared to male patients (p=0.04) (table 2). Figure 5 shows length of hospital stay between the VPSI and LPSI groups. The mean length of hospital stay was 6.2 ±8.5 days for VPSI group compared to 5.4 ±4.2 days in the LPSI group (p = 0.9). Follow up was achieved in 53 (64%) of patients who were discharged, with a mean follow up duration of 19.2 ±22 months. Of these patients, 15 (18%) were followed up telephonically

Mortality

A total of 15 (18%) patients died of which 8 (15%) were in-hospital deaths at IALCH and 7 (8.4%) were reported to have died on follow-up. The causes of in hospital death were Pneumonia (n=4), septicaemia (n=3) and ventriculitis (n=1). The cause of death was not known in the patients who died outside of IALCH as these were followed up telephonically.

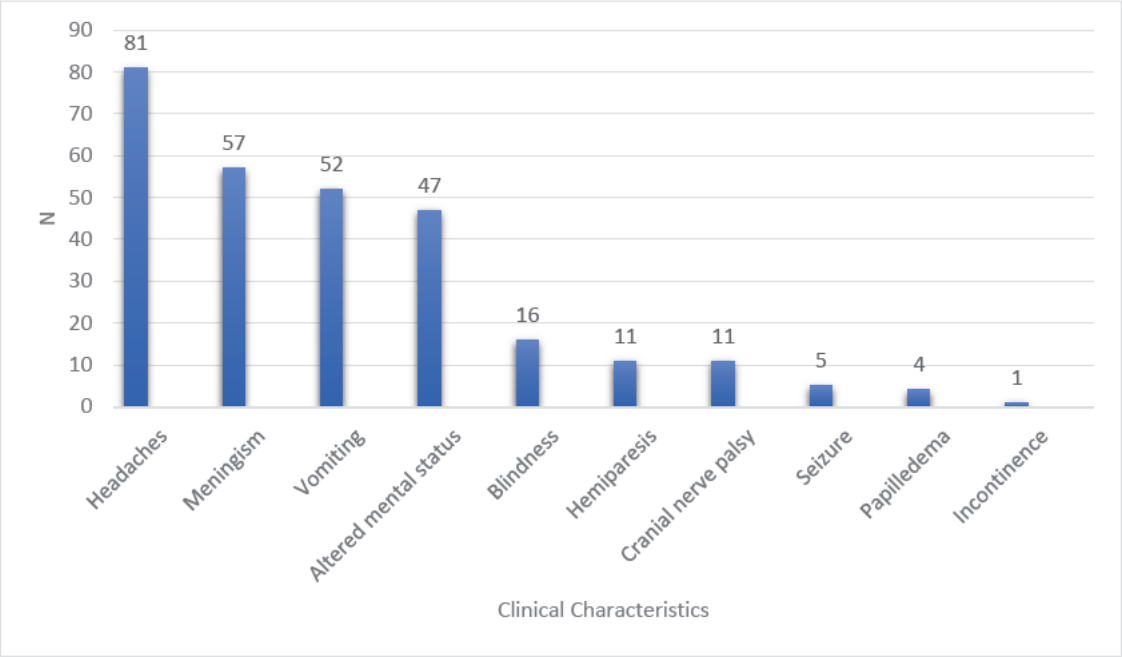

Figure 1: Clinical presentations of HIV positive adult patients shunted for refractory intracranial hypertension secondary to cryptococcal meningitis

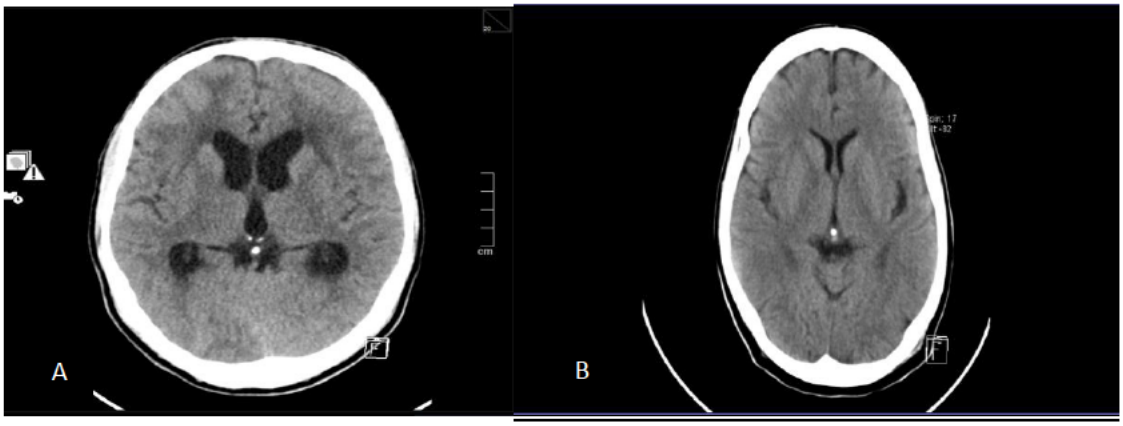

Figure 2: Non-contrasted CT brain scan of typical HIV patients with intracranial hypertension secondary to cryptococcal meningitis showing dilated ventricles (A) and normal sized ventricles (B)

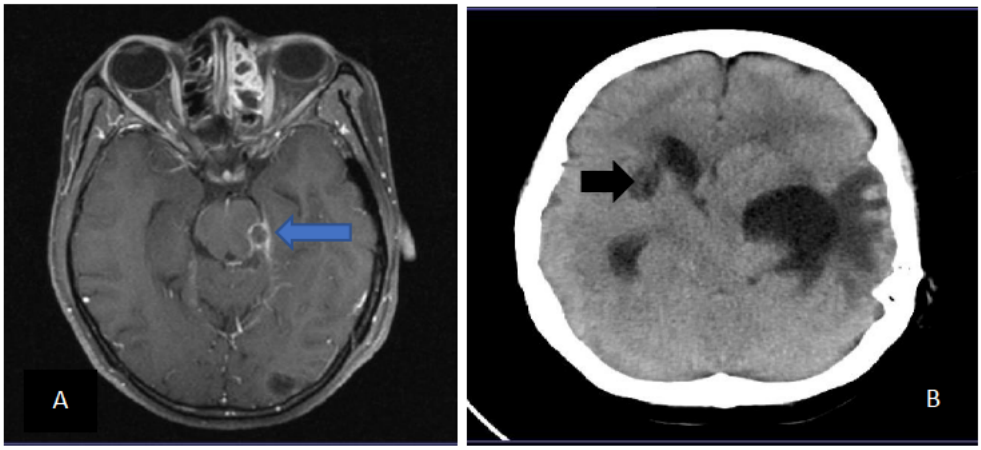

Figure 3: Post contrast T1W MRI brain scan (A) depicting a contrast enhancing inflammatory mass lesion (blue arrow), and a non-contrasted CT brain scan (B) depicting right anterior limb of internal capsule infarct (black arrow).

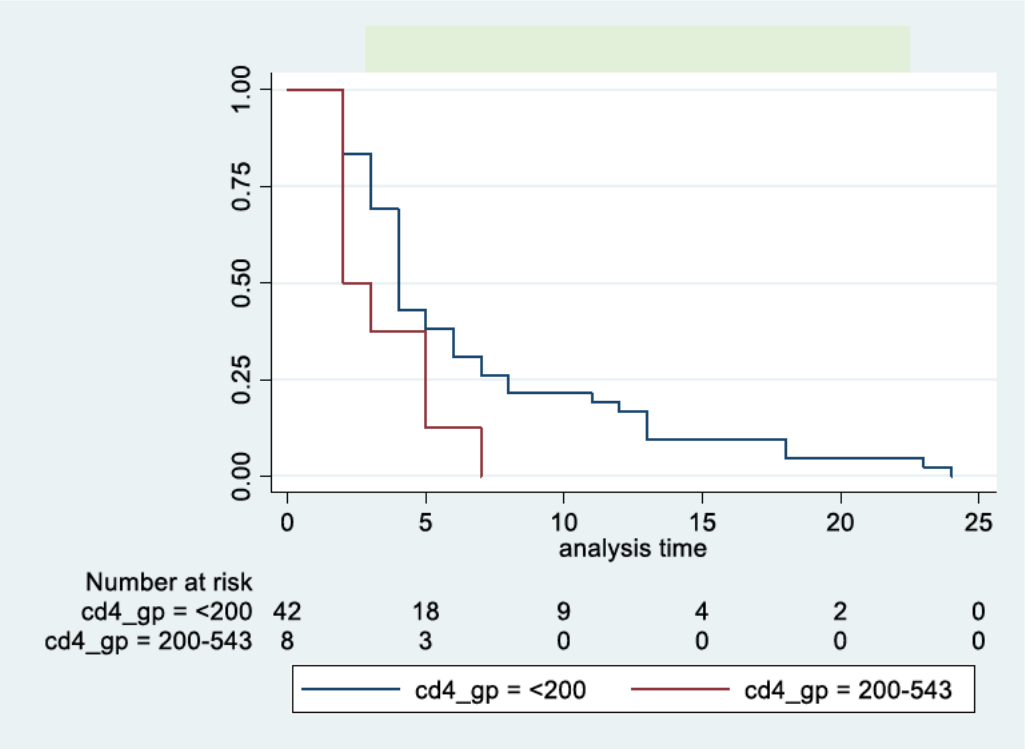

Figure 4: Kaplan-Meier graph demonstrating shunt survival in the VPSI group (Blue line) versus the LPSI group (Red line). The log-rank test was used to analyse data and showed early shunt malfunction in the LPSI group compared to the VPSI group (p=0.044)

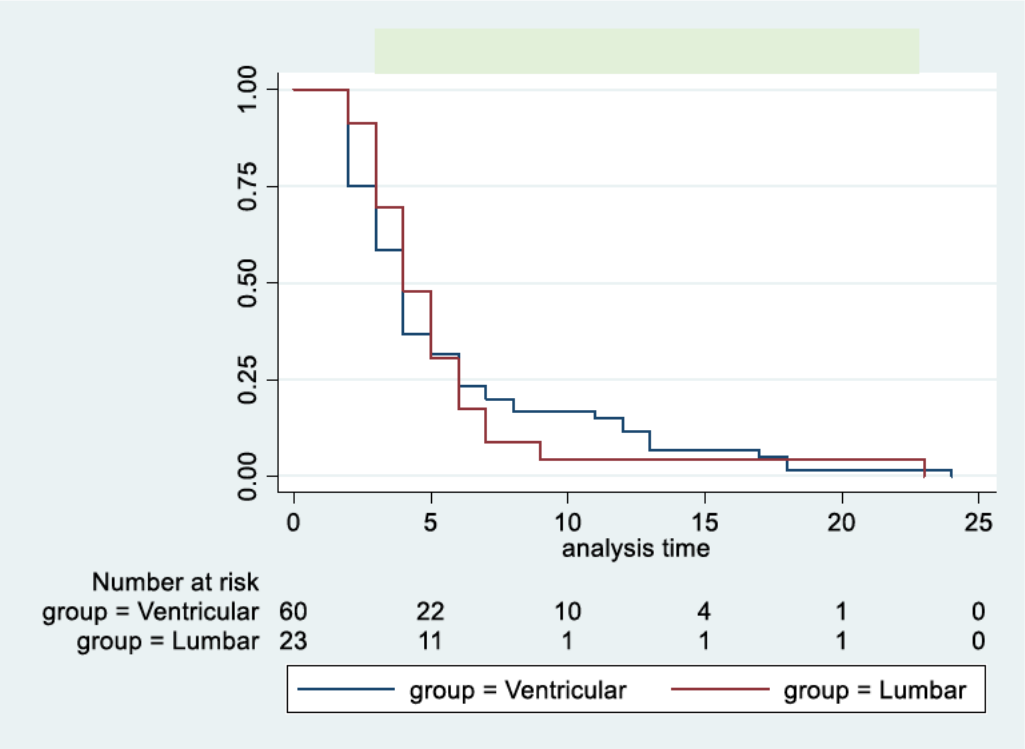

Figure 5: Kaplan-Meier graph demonstrating length of hospital stay in the VPSI group (Blue line) versus LPSI group (Red line). The log-rank test was used to analyse data and showed the mean length of hospital stay was 6.2 ±8.5 days for VPSI group compared to 5.4 ±4.2 days in the LPSI group (p = 0.9)

Table 1: Comparison of demographic profiles and investigations of HIV positive patients shunted for refractory intracranial hypertension secondary to cryptococcal meningitis

Variable	VPSI (n= 60, 72%)	LPSI (n = 23, 28%)	P
Gender (n, %)			
•Male	37 (61.7%)	13 (56.5%)	0.67
•Female	23 (38.3%)	10 (43.5%)	
Age (mean, SD, range)	32.5± 8.6 (18-52)	32.2 ± 6.7 (21-46)	0.89
***OP (mean, SD, range)**	46.9 ±11.6 (14-65)	50.6 ±8.11 (30-65)	0.16
CD4+ (median, IQR)	76 ± (30-129)	54 ± (31-83)	0.45
#ART (n, %)	34 (56.7%)	10 (43.3%)	0.28
ɣHb (mean, SD, range)	11.5 ±2.0 (8.1-14.7)	9.9 ±2.1 (6.5-12.7)	**0.001**
πPlt (median, IQR)	267.5 (218-372.5)	258.0 (177.0-323.0)	0.21
¡WCC (median, IQR)	5.8 (4.4-9.2)	4.8 (3.7-7.3)	0.13
CSF Polymorphs (median, IQR)	0 (0-60)	4 (2.0-14.0)	**0.02**
CSF Lymphocytes (median, IQR)	2.0 (0-18.0)	8.0 (2.0-56.0)	**0.04**
CSF chloride (mean, SD)	122.7 (6.4)	122.3 (6.1)	0.84
CSF glucose (mean, SD)	2.7 (1.1)	2.1 (0.9)	**0.02**
CSF protein (median, IQR)	1.0 (0.3-1.9)	1.1 (0.6-1.2)	0.51
Ventriculomegaly (n, %)	55 (91.7%)	13 (56.5%)	**<0.001**

Age in years *OP: Opening pressure #ART: Antiretroviral therapy ɣHb: Haemoglobin (g/dl) πPlt: Platelets (x10⁹/l) ¡WCC: White cell count (x10⁹/l) CD4+ cells/µl, VPSI:Ventriculo-peritoneal shunt insertion, LPSI: lumbar-peritoneal shunt insertion, IQR: Interquartile range, SD: Standard Deviation, CSF: Cerebrospinal fluid

Table 2: Comparison of the demographic profiles and laboratory data of HIV positive patients with refractory intracranial hypertension secondary to cryptococcal meningitis who developed shunt related complications

Shunt complications (n=27, 31%)	**VPSI (n=17, 28%)**	**LPSI (n=10, 43%)**	**P**
Shunt sepsis (n, %)	8 (48%)	8 (80%)	
• **Age (mean, SD, range)**	32.4 ±7.4 (24-48)	29.9 ±5.7 (21-35)	0.5
Mechanical obstruction (n, %)	9 (52%)	2(20%)	
• **Age (mean, SD, range)**	31.7 ±10.1 (19-52)	33.5 ±7.8 (28-39)	0.8
CD4+ Shunt sepsis (median, IQR)	117 (76-129)	48 (31-66)	**0.03**
CD4+ Mechanical (median, IQR)	30 (16-102)	66.5 (50-83)	0.7
Males	9 (33%)	3 (11%)	**0.04**
Females	8 (30%)	7 (26%)	
CSF Polymorphs (median, IQR)	4 (0-14)	2 (0-4)	0.37
CSF Lymphocytes (median, IQR)	5 (0-56)	2 (0-12)	0.45
CSF glucose (median, IQR)	2.3 (1.1-3.1)	2.5 (1.5-3.0)	0.78
CSF protein (median, IQR)	0.9 (0.6-1.2)	1.4 (0.6-2.7)	**0.07**
[i]WCC (median, IQR)	4.3 (3.1-6.7)	5.9 (4.1-7.71)	0.23
[v]Hb (median, IQR)	8.9 (7.8-10.3)	12.3 (10.2-13.0)	**0.02**
[π]Plt (median, IQR)	305.5 (279-357)	253 (218-337)	0.17

Age in years #ART: Antiretroviral therapy [v]Hb: Haemoglobin (g/dl) πPlt: Platelets (x10⁹/l) [i]WCC: White cell count (x10⁹/l) CD4+ cells/µl VPSI:Ventriculo-peritoneal shunt insertion, LPSI: lumbar-peritoneal shunt insertion, IQR: Interquartile range, SD: Standard Deviation, CSF: Cerebrospinal fluid

Discussion

In our study, more males were affected than females which is similar to reports by other authors (13, 17). This must be viewed in the context that HIV infection in South Africa has been reported to affect more females than males (18-20). The age group reported in our study further re-inforces the fact that the HIV pandemic affected mainly young people who are economically active, thus depriving a country like South Africa of its main workforce required to grow the economy.

In our study, most patients presented with late-stage immunosuppression, with a median CD4+ cell count of 76 cells/ul in the VPSI group and 54 cells/ul in the LPSI group. The WHO defined late stage immunosuppression as a CD4+ cell count of less than 200 cells/µl (6). Baddley et al reported similar findings in their study (17). Cryptococcal Meningitis, along with tuberculous meningitis and coccidioidomycosis, are emblematic for chronic granulomatous meningitis, and are characterised by diffuse lymphocytic meningitis along with foci of inflammation in the basilar meninges (21, 22).

In the setting of AIDS, with the absent host cellular immune response, CM follows a trajectory closer to a massive fungal infestation with overwhelming numbers of cryptococci in the CSF which are thought to obstruct the arachnoid villi directly (9, 23). This may explain why meningism was found in two-thirds of our patients and why headache was the most common clinical feature in this population.

Sixteen (18.3%) of our patients presented with blindness, which is a debilitating complication and often it is not reversible. Lui et al found that blindness caused by optic nerve damage as a result of intracranial hypertension may be reversible following diversion of CSF (16). Forty-four (53%) patients were on ART, and this has to be viewed in the context that in 2002, ARTs were not freely available to patients in SA. Access to ART has improved over the years in SA with quoted figures of 59 000 patients on ART in 2005 and 144 000 patients on ART in 2015 (20, 24).

In KZN, Nadvi et al from 1995 to 2000 prospectively compared 15 HIV positive and 15 HIV negative patients requiring VPSI for TBM and found that HIV positive patients were associated with worse outcomes with a mortality rate of 66.7% (n = 10/15) when compared to 26.7% (n =4/15) in the HIV negative patients (25). A similar study in 2016 by Harrichandparsad et al comparing 15 HIV positive patients on ART and 15 HIV positive patients not on ART found a

similar mortality rate of 67.7% (n= 10/15) in the group not on ART and 26.7% (n = 4/15) in the group on ART (26).

In our study, we found inflammatory lesions in 10 (12%) patients which is similar to what Khan et al found in their series (27). Dilated ventricles were found in 72 (86.7%) patients followed by normal sized ventricles in 15 (18%). This finding is important because CM is known not to cause dilatation of ventricles. This is due to the coating of the ependymal tissue by cryptococcal capsular polysaccharides leading to failure of the ventricles to dilate following increase in the volume of CSF. Our findings, however, differed from Tan et al who found that despite elevated LP opening pressures, the majority of patients did not demonstrate dilated ventricles on CT scan (28).

Dilated ventricles on CT brain scan was an important factor in our unit when determining the type of CSF shunting procedure to be performed. When the ventricles were dilated, the treating neurosurgeon preferred VPSI as the ventricles were easy to cannulate when compared to normal sized or small ventricles, where LPSI was preferred. However, navigation has made it easier and safer for Neurosurgeons to insert VPS even in the setting of small ventricles. A study of 49 patients by Yim et al found that the use of neuro-navigation in the placement of ventricular catheters in patients with small ventricles achieved a 90% (n= 44/49) correct placement position (29).

Most studies reporting on surgical management of intracranial hypertension associated with CM used VPSI (13-17), showing a trend of preference of VPSI over LPSI by most authors. Our study showed a higher rate of shunt complications in the LPSI group versus the VPSI group. This finding is in-keeping with reports by Menger et al who found that LPSI have a significantly higher failure and revision rate of 7% when compared to a VPSI rate of 3.9%. They also reported a longer length of hospital stay in the LPSI group when compared to the VPSI group (30).

Studies comparing VPSI versus LPSI in the treatment of intracranial hypertension, tend to favour the former over the later due to higher complication and revision rates in the LPSI groups (30-32). Abubaker et al found a higher revision rate of 60% in the LPSI group compared to 30% in the VPSI group (31). Tarnaris et al found a 24% complication rate in the LPSI group compared to 11% in the VPSI group (32).

Sharma et al (33) and Choksey et al (34) found that shunt infection rates in HIV-infected individuals were unacceptably high. The overall rate of VPS infection in non-HIV infected

individuals is reported at 1-5%, however in HIV positive individuals, this ranges between 5-15% and some authors have described higher rates at 7-12% (34).

A study by Calvo et al showed that patients with reduced immunity are at a higher risk of post-operative infection in comparison to non-immunocompromised patients (35). A similar finding was made by Woodworth et al (36). Reasons for reluctance to shunt these patients includes higher rates of colonization of the shunt, the theoretical risk of seeding of the fungal spores into peritoneum and shunt obstruction due to high titres of fungal polysaccharide (37).

The most common isolated organisms among our study population were staphylococcus epidermidis and staphylococcus aureus. Staphylococcus species is by far the most common organism responsible for shunt infections accounting for up to 90% of all isolated organisms (34, 38-40). A potential option in mitigating this complication is with the use of Antibiotic-impregnated shunts (AIS). A study performed by Govender et al in Durban KZN evaluating AIS found a 5% infection rate in patients undergoing AIS compared to a 13.3% infection rate in patients undergoing normal shunts (40). A mortality rate of 18% was found in our study which was similar to the mortality rate reported by Cherian et al (13).

Limitations

As a retrospective study, management decisions are assessed after the fact and bias in the treating surgeon cannot be accounted for. Patients referred to the DoN come from various regional and district hospitals all over the province and upon discharge, continuous follow-up can be a challenge.

This study focused on patients in the public sector and did not include the private and therefore might not give a true reflection of the overall prevalence and outcomes of patients managed in KZN.

Conclusion

This study showed that patients with a low CD4+ cell count had an increased rate of shunt complications. LPSI were associated with a higher rate of shunt complication especially in those with low CD4+ cell counts. In a country with high burden of HIV/AIDS, CSF diversion is still an important option for treating refractory intracranial hypertension secondary to HIV associated CM. Access to ART, prevention, early diagnosis and treatment of CM are vital in the prevention of complications to related to this infectious disease.

Conflict of interest

Authors had no conflict of interest when preparing this manuscript.

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Appendices

Appendix 1: The final Study Protocol

Study Protocol

Surgical outcomes of HIV seropositive adult patients with intracranial hypertension secondary to Cryptococcal Meningitis

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Contents

1. Introduction

Meningitis is a serious condition and is a common complication found among the majority of both HIV-positive and negative patients leading to increased morbidity and mortality (1, 2). Cryptococcal meningitis is among the most common opportunistic infections found in HIV positive patients more especially in HIV epidemic areas and the majority of Cryptococcal meningitis infections have been reported in Sub-Saharan Africa (3, 4).

Intracranial hypertension is a common finding among these patients and a percentage of these patients will require diversion of CSF. Early identification and management is very important in order to reduce the morbidity and mortality due to Cryptococcal meningitis thus reducing the burden of illness in a resource limited setting (5)

2. Title of the study

Surgical outcomes of HIV seropositive adult patients with intracranial hypertension secondary to Cryptococcal Meningitis.

3. Research Question

What are the outcomes of surgical management of HIV seropositive adult patients with cryptococcal meningitis presenting with intracranial hypertension.

4. Aim of the study

To assess the management and outcomes of patients admitted with intracranial hypertension due to Cryptococcal Meningitis at the Department of Neurosurgery at Inkosi Albert Luthuli Central Hospital.

5. Specific objectives

1. To review the total admissions of patients with Cryptococcal meningitis.
2. To assess the demographics of patients with Cryptococcal meningitis.
3. To document the clinical presentations.
4. To document the presence or absence of neurological deficits.
5. To document the neuradiological findings.

6. To document the CD4 count.

7. To document the HIV viral load.

8. To assess the type of CSF diversion used, LP shunt vs VP shunt.

9. To document the surgical complications.

10. To document the complications among these patients.

11. To provide recommendations to management and improvement of outcomes to patients admitted with cryptococcal meningitis.

6. Background and Literature review

HIV/AIDS is one of the world's most serious health and developmental challenges. There were approximately 36.7 million people worldwide living with HIV/AIDS at the end of 2015. Of these, 1.8 million were children less than 15 years old (6). The HIV pandemic is most severe in Sub-Saharan Africa with over 60% of people living with HIV/AIDS living in this region.

Statistics South Africa 2017 statistics reported an overall HIV prevalence rate of approximately 12.7% of the South African population. The total number of people living with HIV is estimated at 7.03 million at the end of 2016. For adults 15-49 years, an estimated 18.9% of the population is HIV positive (7). This therefore will equate to a significant utilization of the healthcare budget.

Cryptococcal meningitis is caused by infection with the encapsulated yeast Cryptococcus neoformans especially in patients with reduced cell-mediated immunity. Cryptococcosis represents a major life-threatening fungal infection in patients with severe HIV infection and may also complicate organ transplantation, reticuloendothelial malignancy, corticosteroid treatment, or sarcoidosis.

Cryptococcus neoformans is a major cause of illness in people living with HIV/AIDS, with an estimated 220,000 cases of cryptococcal meningitis occurring worldwide each year resulting in nearly 181,000 deaths (8).

Before the discovery of antiretroviral therapy, fungal and other opportunistic infections were a major problem for people with advanced HIV/AIDS. Since then the numbers of fungal infections

and deaths due to fungal infections in people with advanced HIV/AIDS have decreased substantially in the US and other developed countries. Although the widespread availability of antiretroviral therapy cryptococcal meningitis is still a major problem in resource limited countries where HIV prevalence is high and access to healthcare is limited (5).

Most cryptococcal meningitis cases occur in sub-Saharan Africa and is the most common cause of meningitis in adults (9-11). Cryptococcal meningitis is therefore one of the leading causes of death in HIV/AIDS patients in sub-Saharan Africa, where it may kill more people each year than tuberculosis.

A local study on cryptococcal meningitis demonstrated during a 4 year study period 65 patients with cryptococcal meningitis and 44(68%) were HIV infected (12).

The pathophysiology of cryptococcal meningitis is well documented. There are more than 50 species that comprise the genus Cryptococcus but human disease is primarily associated with Crytococcus neoformans and Cryptococcus gatti. The pathogenesis of cryptococcosis depends mainly with the normal functioning of host defence mechanisms. Transmission is mainly by the respiratory route and not directly from human to human (13).

The symptoms of cryptococcal meningitis are usually subacute or chronic in nature and majorly associated with elevated intracranial pressure. One study demonstrated that more than 10% of patients had opening pressures of more than 25cmH20 on initial LP (14).

Common symptoms include headache, confusion, lethargy, obtundation, coma, nausea and vomiting, visual disturbances, fever and neck stiffness, hearing defects, seizures, gait abnormalities and choreoathetoid movements. Several mechanisms have been implicated in the development of elevated intracranial pressure in cryptococcal meningitis mainly obstruction of outflow of CSF by blockage of the arachnoid villi, and fungal polysaccharide aggregation in the arachnoid villi and subarachnoid spaces (15).

The diagnosis of cryptococcal meningitis includes obtaining cerebrospinal fluid for India ink smear, fungal culture and cryptococcal antigen testing. A computed tomography or magnetic resonance imaging scan should be done prior to performing a lumbar puncture in patients presenting with focal neurological deficits or a history of slowly progressive meningitis. Studies have however demonstrated that despite elevated opening pressures, the majority of patients do

not demonstrate ventriculomegaly on CT scan (16). The mechanism for this is not clear, but some authors have suggested that cryptococcal capsular polysaccharides coating the surfaces of the brain, as well as within the parenchyma, lead to a situation in which the internal structures cannot compensate for the increase in the volume of CSF.

Treatment for cryptococcal meningitis in patients with HIV/AIDS includes Amphotericin B deoxycholate, 0.7-1 mg/kg/day for 2 weeks, with or without Flucytosine, 100 mg/kg/day in 4 divided doses for 2 weeks. After 2 weeks, fluconazole at 400 mg/day for a minimum of 8-10 weeks (17-19). Alternative initial therapies include Liposomal amphotericin B 3-4 mg/kg/day for at least 2 weeks in patients at risk for renal dysfunction. In patients intolerant of amphotericin B products, fluconazole 800-1200 mg/day plus flucytosine 100 mg/kg/day for at least 6 weeks can be used. Initial therapy should be considered successful only after CSF culture is negative for cryptococcal organisms and the patient has had significant clinical improvement. Guidelines published in 2010 support discontinuation of Fluconazole 200mg daily for life when the CD4 count exceeds 100 cells/μL and HIV viral load is undetectable or very low for more than 3 months. However, reinstitution of maintenance therapy should be considered if the CD4 cell count falls to less than 100 cells/μL (20).

Elevated CSF pressure among these patients remains a problem necessitating daily spinal taps to control the pressures. Control of CSF pressure is critical to the patient's survival. An initial opening pressure of 25 cm H2O or greater must be reduced and kept around 20 cm H2O throughout therapy. Failure to control CSF pressure may result in blindness, permanent neurologic deficits, or death. The majority of patients with persistently elevated opening pressures will require diversion of CSF in the form of repeat spinal taps, lumbar drainage or ventricular shunts.

The largest series in which permanent diversionary shunts were placed for the management of intracranial hypertension secondary to cryptococcal meningitis in primarily HIV positive patients was conducted by Cherian et al (21). Shunts were considered in patients who did not obtain adequate relief of headache after lumbar puncture drainage, had persistently elevated opening pressures after at least 3 lumbar taps or could no longer tolerate lumbar puncture. A total of 50 patients were identified with cryptococcal meningitis, 13(26%) were treated with shunts, 16 (32%) treated with serial LP and 21 (42%) treated with medical therapy only. 2 out of 13 (15%) mortality

was reported in comparison to 8/31(22%) mortality in those treated with medical therapy and serial LPs alone.

There currently is no available literature in the KwaZulu Natal Province on shunting in patients with cryptococcal meningitis and this study aims to provide local statistics with regard to the management and outcomes as well as improving the morbidity and mortality among these patients.

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8. Study design

a. Study population

This will be a retrospective analysis of data collected from charts of all HIV positive consecutive patients with a diagnosis of cryptococcal meningitis managed during the period of January 2003 to January 2015 at the Department of Neurosurgery at Inkosi Albert Luthuli Central Hospital. This is the only Neurosurgical unit in the province. The study population will include patient demographics such as age groups, sex, HIV positive patients, all of whom were managed at this institution.

b. Inclusion/exclusion criteria

All adult patients diagnosed with Cryptococcal meningitis who were referred to the Department of Neurosurgery at IALCH will be included in this study.

HIV negative patients and patients with meningitis caused by other organisms will be excluded from the study. Patients with incomplete medical records, laboratory, radiological and serological records will also be excluded.

c. Data collection methods and tools

Data will be collected from the electronic files of patients archived on Meditech™ which is the software utilized at IALCH. A senior research Librarian at the Nelson R Mandel School of Medicine will be consulted for the most recent database updated concerning relevant literature. A data collection tool will be used to enter patient's details including characteristics such as; age, gender, referral hospital, HIV status, CD4 count, lumbar puncture findings and opening pressure, level of consciousness on admission, symptoms, neurological deficits, radiological findings, treatment modality, time to surgical treatment, surgical complications, length of hospital stay, clinical outcomes as measures by the GOS and mortality rate.

The parameters will be entered into a Microsoft Excel® spreadsheet and statistical analysis will be performed.

d. Search strategy

Electronic search engines will be used to identify the most relevant literature. Search engines and databases that will be utilized include:

Pubmed

Google Scholar

Clinical Key

Medline

EBSCO host

English language literature will be utilized

Key words such as "Cryptococcal meningitis", "HIV/AIDS", "Shunting", "Intracranial Hypertension", "Immunocompromised", "Global statistics", "Management protocols" and "Surgical Outcomes" were used to find literature of relevance.

e. Data analysis technique

Data analysis will be performed with the assistance of the biostatistician Catherine Connolly. A sample size of 100 is required to estimate mortality in patients admitted to the Department of Neurosurgery with Cryptococcal Meningitis to within 15% with a probability of 95% and assuming 50% mortality.

Descriptive statistics will be used to summarize demographic and clinical characteristics of patients. Frequency distribution of numeric data will be examined for normality and means or medians used as appropriate. Categorical factors such as sex, co-morbidity, associated with mortality will be identified using Chi square tests. Numeric data such as age, opening pressures will be compared using T-test or Wilcoxon tests as appropriate. Factors significant at the bi variate level will be included in a logistic regression model to identify independent risk factor association with mortality.

Data will be analysed in Stata v13 and a p value of 0.05 will be considered statistically significant.

9. Study location

This study will be conducted at a single centre which is the Department of Neurosurgery at Inkosi Albert Luthuli Central Hospital situated in Durban, KwaZulu Natal, South Africa.

10. Study period

January 2003 to January 2015

11. Limitations of the study

This is a retrospective study and therefore amongst the limitations, are the varying management decisions taken depending on the treating surgeon resulting in bias.

Another limitation of this study is the incomplete follow up of patients due to various reasons which will result in incomplete follow up data. Patients referred to the Neurosurgery are usually referred from various regional and district hospital and upon discharge, no proper follow up protocol exists on their side.

This study will also focus on patients in the public sector and not the private and therefore this study might not give a true reflection of the overall prevalence and outcomes of patients managed in KwaZulu Natal.

12. Ethical considerations

Ethical approval will be sought from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal. The study will be conducted in full accordance with the principles and Declaration of Helsinki and good clinical practice and regulations of BREC. This is a retrospective study so there will be no direct contact with the patients and patient details will be kept private and confidential.

13. Addendum A: Data collection tool

Data collection tool

Sample number:

1. Age		
2. Gender		
3. CSF diagnosis	C.neoformans	
	C.gatti	
4. Clinical presentations	Headache	
	Nausea	
	Vomiting	
	Altered mental status	
	Seizures	
	Meningism	
5. Signs on clinical examination	Hemiparesis/hemiplegia	
	Pupillary reflex	
	Others	
6. GCS on admission		

7. CT scan findings	Ventriculomegaly	
	Obstructive hydrocephalus	
	Infarcts	
	No change	
8. HIV status	Reactive	
	Non-reactive	
9. CD4 count		
10. Opening pressure		
11. Medical management	Amphotericin B	
	Fluconazole	
	Flucytocine	
	Steroids	
12. Surgical management	Serial LP	
	Lumbar drain	
	VP shunt	
	LP shunt	
	None	
13. Time to surgery		
14. Delay before surgery		
15. Surgical complications		
16. Length of hospital stay		
17. Mortality		
18. GOS at discharge		

Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript

GUIDE FOR AUTHORS

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World Neurosurgery has an open access mirror journal, *World Neurosurgery: X*.

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that:

One author has been designated as the corresponding author with contact details:

• E-mail address

• Full postal address

Please note that it is our journal policy to only permit one author to be listed as the corresponding author for an article. Please avoid listing multiple corresponding authors on your title page or manuscript.

Please ensure that the following items are present.

Required files to be uploaded:

• Cover Letter

• Title Page (see 'Essential title page information' section for further details) containing: title, all authors' complete names, all authors' highest academic degree and affiliations, corresponding author name and contact details, key words (3 to 7) and short/running title

• Manuscript

• Disclosure-Conflict of Interest

• Abbreviation List

• Figures, if applicable

• Tables, if applicable.

Further considerations:

• Manuscript has been 'spell checked' and 'grammar checked'

• All references mentioned in the Reference List are cited in the text, and vice versa

• Permission has been obtained for use of copyrighted material from other sources (including the Internet)

• A competing interests statement is provided, even if the authors have no competing interests to declare

• Journal policies detailed in this guide have been reviewed

• Referee suggestions and contact details provided, based on journal requirements

For further information, visit our Support Center.

PREPARATION

Cover Letter

Cover Letter Info to include the following: The author(s) should provide a cover letter with each submission, ensuring they include the following: A statement of non-duplication, with the following
statements: "I, (corresponding author's name), certify that this manuscript is a unique submission and is not being considered for publication, in part or in full, with any other source in any medium."

Peer review

This journal operates a single blind review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of three independent expert reviewers to assess the scientific quality of the paper (except for Case Reports, which only require one review). The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. More information on types of peer review.

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. When preparing your submission please double space the entire document with 1" margins. Each page should be numbered, with the first author's last name in the upper right hand corner. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier: https://www.elsevier.com/guidepublication). Note that source files of figures, tables
and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.

To avoid unnecessary errors, you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

Subdivision - unnumbered sections

Divide your article into clearly defined sections. Each subsection is given a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross referencing text: refer to the subsection by heading as opposed to simply 'the text'.

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Results

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices

If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information

• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.

• ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lowercase superscript letter immediately after the author's name and in front of the appropriate address.

Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.

• ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**

• ***Present/permanent address.*** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

• ***Highest academic degrees for all authors.*** Degrees are not listed in the author line but are necessary for other purposes.

• ***Departmental and institutional affiliations for all authors.*** When providing author names and affiliations, be sure to include department/division information and not only the institution.

• ***Key words (3 to 7).*** Provide an alphabetized list of 3 to 7 key words which will appear in print and used for indexing purposes.

• ***Short title.*** Short titles are required for all article types except for Letters to the Editor, Technical Notes and invited articles. The short title should be 40 characters or less, including spaces.

Abbreviations list

Provide an alphabetized list of all abbreviations used in the article, with each abbreviation/acronym followed by its complete spell out.

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the

research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself. Abstracts should be 250 words, maximum.

Original Articles, Doing More With Less, Women in Neurosurgery, Great Hospitals, Neurosurgery

Nursing and Technical Notes require a structured abstract with the following headings: **Objective (or Background), Methods, Results, Conclusions**.

Case Reports require a structured abstract with the following headings: **Background, Case Description, Conclusions**.

Historical Vignettes and Literature Reviews require an abstract, but it can be unstructured (no headings).

Clinical Images require a 50-150 word unstructured abstract (no headings).

Video Articles require a 250 word unstructured abstract.

Graphical abstract

Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. You can view Example Graphical Abstracts on our information site.

Authors can make use of Elsevier's Illustration Services to ensure the best presentation of their images and in accordance with all technical requirements.

Graphical Abstracts are optional for the following article types: Original Articles, Doing More With Less, Women in Neurosurgery, Great Hospitals, Neurosurgery Nursing, Technical Notes, Case Reports, Historical Vignettes, Literature Reviews, Clinical Images, Video Articles.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Formatting of funding sources

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, please include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Units
Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Math formulae
Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).
Embedded math equations
If you are submitting an article prepared with Microsoft Word containing embedded math equations then please read this (related support information).
Artwork
Electronic artwork
General points
• Make sure you use uniform lettering and sizing of your original artwork.
• Embed the used fonts if the application provides that option.
• Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.
• Number the illustrations according to their sequence in the text.
• Use a logical naming convention for your artwork files.
• Provide captions to illustrations separately.
• Size the illustrations close to the desired dimensions of the published version.
• Submit each illustration as a separate file.
• Ensure that color images are accessible to all, including those with impaired color vision.
A detailed guide on electronic artwork is available.
You are urged to visit this site; some excerpts from the detailed information are given here.
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If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format.
Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):
EPS (or PDF): Vector drawings, embed all used fonts.
TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.
TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.
TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.
Please do not:
• Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
• Supply files that are too low in resolution;
• Submit graphics that are disproportionately large for the content.
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Figure captions

Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Number tables consecutively in accordance with their appearance in the text. Each table requires its own title. All tables should be placed in their own file, separate from the manuscript file. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article. Place footnotes to tables below the table body and indicate them with the following symbols in the following order:

- * (asterisk)
- † (dagger)
- ‡ (double dagger)
- § (section mark)
- II (parallel mark)
- ¶ (paragraph symbol)
- # (number sign)
- ** (etc.)
- *** (etc.)

All studies listed in a table must be cited in the table and included in the complete reference list, just as if the study in question were discussed and cited in the text of the article.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Reference links

Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as

Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.
A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, https://doi.org/10.1029/2001JB000884.
Please note the format of such citations should be in the same style as all other references in the paper.
Data references
This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.
References in a special issue
Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.
Users of Mendeley Desktop can easily install the reference style for this journal by clicking the following link:
http://open.mendeley.com/use-citation-style/world-neurosurgery
When preparing your manuscript, you will then be able to select this style using the Mendeley plugins for Microsoft Word or LibreOffice.
Reference style
Text: Indicate references by (consecutive) superscript arabic numerals in the order in which they appear in the text. The numerals are to be used *outside* periods and commas, *inside* colons and semicolons. For further detail and examples you are referred to the AMA Manual of Style, A Guide for Authors and Editors, Tenth Edition, ISBN 0-978-0-19-517633-9.
List: Number the references in the list in the order in which they appear in the text.
Examples:
Reference to a journal publication:
1. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. *J Sci Commun.* 2010;163:51–59. https://doi.org/10.1016/j.Sc.2010.00372.
Reference to a journal publication with an article number:
2. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. *Heliyon*. 2018;19:e00205. https://doi.org/10.1016/j.heliyon.2018.e00205.
Reference to a book:
3. Strunk W Jr, White EB. *The Elements of Style.* 4th ed. New York, NY: Longman; 2000.
Reference to a chapter in an edited book:
4. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith
RZ, eds. *Introduction to the Electronic Age.* New York, NY: E-Publishing Inc; 2009:281–304.
Reference to a website:

5. Cancer Research UK. Cancer statistics reports for the UK. http://www.cancerresearchuk.org/ aboutcancer/statistics/cancerstatsreport/; 2003 Accessed 13 March 2003.
Reference to a dataset: [dataset] 6. Oguro, M, Imahiro, S, Saito, S, Nakashizuka, T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. https://doi.org/10.17632/ xwj98nb39r.1.

Journal abbreviations source

Journal names should be abbreviated according to the List of Title Word Abbreviations.

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Supplementary material such as applications, images and sound clips, can be published with your article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Please submit your material together with the article and supply a concise, descriptive caption for each supplementary file. If you wish to make changes to supplementary material during any stage of the process, please make sure to provide an updated file.

Do not annotate any corrections on a previous version. Please switch off the 'Track Changes' option in Microsoft Office files as these will appear in the published version.

Research data

This journal encourages and enables you to share data that supports your research publication where appropriate, and enables you to interlink the data with your published articles. Research data refers to the results of observations or experimentation that validate research findings. To facilitate reproducibility and data reuse, this journal also encourages you to share your software, code, models, algorithms, protocols, methods and other useful materials related to the project.

Below are a number of ways in which you can associate data with your article or make a statement about the availability of your data when submitting your manuscript. If you are sharing data in one of these ways, you are encouraged to cite the data in your manuscript and reference list. Please refer to the "References" section for more information about data citation. For more information

on depositing, sharing and using research data and other relevant research materials, visit the research data page.

Data linking

If you have made your research data available in a data repository, you can link your article directly to the dataset. Elsevier collaborates with a number of repositories to link articles on ScienceDirect with relevant repositories, giving readers access to underlying data that gives them a better understanding of the research described.

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For supported data repositories a repository banner will automatically appear next to your published article on ScienceDirect.

In addition, you can link to relevant data or entities through identifiers within the text of your manuscript, using the following format: Database: xxxx (e.g., TAIR: AT1G01020; CCDC: 734053; PDB: 1XFN).

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This journal supports Mendeley Data, enabling you to deposit any research data (including raw and processed data, video, code, software, algorithms, protocols, and methods) associated with your manuscript in a free-to-use, open access repository. During the submission process, after uploading your manuscript, you will have the opportunity to upload your relevant datasets directly to *Mendeley Data*. The datasets will be listed and directly accessible to readers next to your published article online.

For more information, visit the Mendeley Data for journals page.

Appendix 3: Ethical approvals

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3180/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

HRKM Ref: 119/18
NHRD Ref: KZ_201803_025

Date: 4 April 2018
Dear Dr NS Mabovula (IKZN)

Approval of research

1. The research proposal titled **'Surgical outcomes of HIV seropositive adult patients with intracranial hypertension secondary to Cryptococcal Meningitis'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

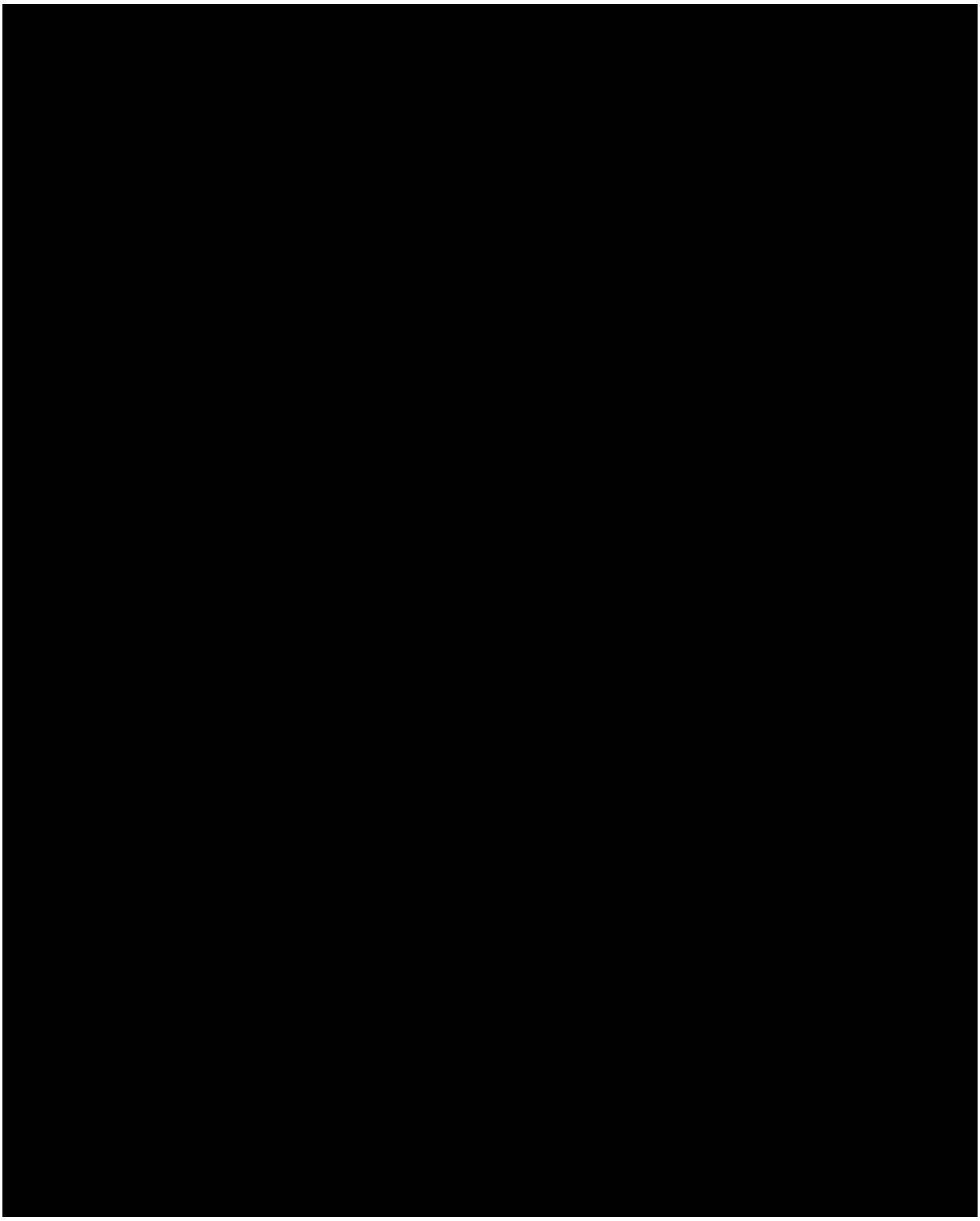
3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]
Dr E Lutge
Chairperson, Health Research Committee
Date: 04/04/18

Fighting Disease, Fighting Poverty, Giving Hope



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RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
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Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

10 December 2018

Dr NS Mabovula (217079573)
School of Clinical Medicine
College of Health Sciences
ndyebomabovula@yahoo.co.uk

Dear Dr Mabovula

Protocol: Surgical outcomes of HIV seropositive adult patients with intracranial hypertension secondary to cryptococcal Meningitis.
Degree: MMed
BREC Ref No: BE060/18 (sub-study of BCA 219/15)

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	08 February 2019
Expiration of Ethical Approval:	07 February 2020

I wish to advise you that your application for Recertification received 05 December 2018 for the above protocol has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 11 December 2018.

Yours sincerely

[redacted]

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc: Jantjies@ukzn.ac.za basilenicker@yahoo.com

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

1 March 2018

Dr N S Mabovula
School of Clinical Medicine
College of Health Sciences

Dear Dr Mabovula

Re: Approved Research: Ref No: BE060/18: Surgical outcomes of HIV seropositive adult patients with intracranial hypertension secondary of cryptococcal meningitis.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langalibalele Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

[redacted]

Dr L P Mtshali
Medical Manager

Fighting Disease, Fighting Poverty, Giving Hope

Appendix 4: Data collection tools

Data was collected from the electronic files of patients archived on Meditech™ which is the software utilized at IALCH. A senior research Librarian at the Nelson R Mandel School of Medicine will be consulted for the most recent database updated concerning relevant literature. A data collection tool will be used to enter patient's details including characteristics such as; age, gender, referral hospital, HIV status, CD4 count, lumbar puncture findings and opening pressure, level of consciousness on admission, symptoms, neurological deficits, radiological findings, treatment modality, time to surgical treatment, surgical complications, length of hospital stay, clinical outcomes as measures by the GOS and mortality rate.

The parameters were entered into a Microsoft Excel® spreadsheet and statistical analysis will be performed.

Data collection tool

Sample number:

19. Age		
20. Gender		
21. CSF diagnosis	C.neoformans	
	C.gatti	
22. Clinical presentations	Headache	
	Nausea	
	Vomiting	
	Altered mental status	
	Seizures	
	Meningism	
23. Signs on clinical examination	Hemiparesis/hemiplegia	
	Pupillary reflex	
	Others	
24. GCS on admission		

25. CT scan findings	Ventriculomegaly	
	Obstructive hydrocephalus	
	Infarcts	
	No change	
26. HIV status	Reactive	
	Non-reactive	
27. CD4 count		
28. Opening pressure		
29. Medical management	Amphotericin B	
	Fluconazole	
	Flucytocine	
	Steroids	
30. Surgical management	Serial LP	
	Lumbar drain	
	VP shunt	
	LP shunt	
	None	
31. Time to surgery		
32. Delay before surgery		
33. Surgical complications		
34. Length of hospital stay		
35. Mortality		
36. GOS at discharge		

Appendix 5: Raw data

Numerica	Age	Gender	Clinical pr	GCS on ad	CT scan fir	HIV status	HAART	CSF diagn	CD4 count	Opening p	Medical M	Surgical M	Time to su	Mortality	Length of	GOS at dis
CCM001	48	f	A1,A2,A3,	13	V1,V3	P	no	C1	123	35	M1,M2	S3	14	0	18	3
CCM002	40	f	A1,A2,A3,	15	V4	P	no	C1	98	40	M2	S3	6	0	8	5
CCM003	32	m	A1,A2,A3,	14	V4	P	no	C1	111	33	M2	S3	6	0	13	5
CCM004	29	m	A1,A2,A5,	15	V4	P	no	C1	76	45	M2	S3	10	0	11	5
CCM009	35	m	A1,A4,A7	13	V1	P	no	C1	50	65	M1,M2	S3	1	0	8	5
CCM010	24	f	A1,A7	15	V1,V2,V3	P	no	C1	16	ND	M1,M2	S3	4	0	63	5
CCM011	24	m	A1,A4,A6,	12	V1	P	yes	C1	7	50	M1,M2	S3	1	0	4	4
CCM012	26	f	A1,A2,A3,	15	V1	P	yes	C1	122	50	M1,M2	S3	1	0	4	5
CCM013	30	f	A1,A4,A7	11	V1,V2	P	yes	C1	170	ND	M1,M2	S3	7	0	13	5
CCM014	45	f	A1	15	V1	P	no	C1	U	38	M1,M2	S3	0	0	6	5
CCM015	34	m	A4,A6,A8	6	V1,V2	P	no	C1	8	11	M1,M2	S5	2	1	8	1
CCM016	29	f	A1,A2,A3,	14	V1	P	yes	C1	6	50	M2	S4	1	0	6	5
CCM017	29	m	A1,A4	9	V1,V2	P	yes	C1	68	ND	M2	S3	0	0	7	5
CCM018	27	m	A1,A4,A6,	12	V1	P	yes	C1	U	40	M2	S3	0	0	3	5
CCM019	32	f	A1,A6,A13	15	V1	P	no	C1	46	50	M1,M2	S3	0	0	2	5
CCM020	33	f	A1,A2,A3,	12	V1	P	yes	C1	U	65	M2	S3	0	0	5	5
CCM021	20	m	A1,A7	15	V1	P	yes	C1	123	28	M2	S3	0	0	3	5
CCM022	21	f	A1,A4	14	V1	P	no	C1	U	50	M1,M2	S3	2	0	3	5
CCM023	29	m	A1,A4,A11	14	V1	P	no	C1	U	50	M1,M2	S3	0	0	2	5
CCM024	34	f	A1,A6,A9	15	V1	P	no	C1	U	40	M1,M2	S3	0	0	4	5
CCM025	37	m	A1,A10,A1	15	V1,V2	P	yes	C1	28	ND	M1,M2	S5	1	0	9	5
CCM026	19	m	A1,A2,A3,	15	V1	P	yes	C1	30	26	M1,M2	S3	1	0	4	4
CCM027	23	m	A1,A4, A6	14	V1	P	no	C1	U	50	M1,M2	S3	0	0	4	4
CCM028	44	m	A1,A2,A3,	14	V1	P	no	C1	21	50	M1	S3	0	0	4	4
CCM029	37	m	A1,A4,A12	14	V1	P	yes	C1	64	50	M1,M2	S3	0	0	4	5
CCM031	39	f	A1,A4,A6,	14	V4	P	yes	C1	50	65	M1,M2	S4	0	0	6	4
CCM032	34	m	A1,A6	15	V1	P	yes	C1	U	50	M1,M2	S3	0	0	2	5
CCM033	31	f	A1,A4,A6,	9	V1	P	yes	C1	18	65	M1,M2	S3	1	0	3	4
CCM035	26	f	A1,A4,A7	13	V1,V2	P	no	C1	78	ND	M1,M2	S5	0	1	6	1
CCM036	43	m	A1,A4,A6,	12	V1	P	yes	C1	220	50	M1,M2	S4	5	1	7	1
CCM038	27	f	A1,A4,A6	14	V1	P	yes	C1	U	55	M1,M2	S3	0	0	6	4
CCM039	39	m	A1,A6	14	V1,V2	P	yes	C1	80	ND	M1,M2	S5	0	1	16	1
CCM040	52	m	A1,A4,A6,	13	V4	P	no	C1	5	60	M1,M2	S3	3	1	18	1
CCM041	38	f	A1,A2,A3,	15	V1	P	yes	C1	U	32	M1,M2	S3	0	0	6	5
CCM042	28	m	A1,A2,A3,	15	V1	P	yes	C1	U	65	M1	S4	0	0	5	5
CCM043	40	f	A1,A4,A6	14	V1	P	yes	C1	68	55	M1,M2	S3	1	0	3	4
CCM044	24	m	A1,A2,A3,	13	V4	P	no	C1	U	60	M1	S4	1	0	6	5
CCM045	44	f	A1,A4,A6,	13	V1	P	yes	C1	U	43	M1	S3	2	0	5	4
CCM047	30	f	A1,A2,A3,	14	V1	P	no	C1	77	50	M1	S3	0	0	3	5
CCM048	24	f	A1,A4,A6	14	V1	P	yes	C1	129	38	M1,M2	S3	0	0	7	4
CCM049	30	f	A1,A2,A3,	14	V1	P	yes	C1	66	50	M1	S4	0	0	3	4
CCM050	37	m	A1,A2,A3,	14	V1	P	no	C1	U	36	M1	S4	2	0	4	5
CCM051	46	m	A1,A6	15	V4	P	no	C1	U	50	M1	S4	2	0	4	5
CCM052	30	f	A1,A4,A6,	12	V4	P	yes	C1	270	50	M1	S4	3	0	5	4
CCM053	33	f	A1,A4,A6	14	V4	P	no	C1	48	55	M1,M2	S4	0	0	5	4
CCM054	37	m	A1,A4,A6	14	V1	P	yes	C1	U	40	M1	S4	1	0	4	5
CCM055	21	f	A1,A2,A3,	14	V1	P	no	C1	11	50	M1	S4	1	0	3	4
CCM056	34	f	A1,A6	15	V4	P	no	C1	U	55	M1	S4	0	0	3	5
CCM057	33	f	A1,A2,A3,	14	V4	P	no	C1	U	50	M1,M2	S4	0	0	3	5
CCM058	25	m	A1,A2,A3,	8	V1	P	no	C1	26	50	M1,M2	S3	0	0	4	3
CCM059	35	m	A1,A4,A6,	14	V1	P	yes	C1	U	37	M1,M2	S3	0	0	2	5
CCM060	28	m	A1,A2,A3,	13	V4	P	yes	C1	83	30	M2	S4	1	0	4	5
CCM061	48	m	A1,A4,A6	14	V1	P	yes	C1	U	33	M1	S3	0	0	4	5
CCM062	42	m	A1,A2,A3,	12	V1	P	no	C1	U	50	M1,M2	S4	0	0	2	4
CCM063	28	m	A1,A2,A3,	12	V1	P	no	C1	U	60	M1,M2	S3	2	0	6	3
CCM064	35	m	A1,A2,A3,	15	V4	P	yes	C1	U	55	M1,M2	S4	0	0	7	5
CCM065	25	f	A1,A2,A3,	15	V1	P	yes	C1	U	50	M1	S4	0	1	2	1
CCM066	28	m	A1,A2,A3,	15	V1	P	no	C1	U	50	M1	S3	0	0	3	5
CCM067	34	m	A1,A4,A6	14	V1	P	yes	C1	54	60	M1	S4	3	0	5	4
CCM068	38	m	A1,A6	15	V1	P	no	C1	240	60	M1	S3	0	0	2	5
CCM069	34	m	A1,A4,A9	14	V1	P	yes	C1	456	50	M1,M2	S3	0	0	2	5
CCM070	33	m	A1,A2,A3,	15	V1	P	yes	C1	182	30	M1	S3	0	0	2	5
CCM071	47	m	A1,A6,A7	14	V1,V2	P	yes	C1	113	ND	M1	S3	0	0	2	4
CCM072	25	m	A1,A6,A9	14	V1	P	yes	C1	U	50	M1,M2	S4	0	0	3	5
CCM073	39	f	A1,A6,A13	15	V1	P	no	C1	10	50	M1	S3	2	0	4	5
CCM074	18	m	A1,A2,A3,	15	V1	P	yes	C1	523	55	M1	S3	0	0	5	5
CCM075	35	m	A1	15	V1	P	yes	C1	U	50	M1	S4	0	0	9	5
CCM076	18	m	A1,A2,A3,	14	V1	P	yes	C1	12	65	M2	S3	0	0	2	5
CCM077	21	f	A1,A4,A6,	14	V1	P	yes	C1	31	50	M1,M2	S4	1	0	4	5
CCM078	41	m	A1,A4,A6,	13	V1,V2	P	no	C1	U	ND	M2	S3	0	0	17	4
CCM080	29	m	A1,A6A,A	15	V1	P	yes	C1	U	40	M1,M2	S3	0	0	4	5
CCM081	35	f	A1,A4,A6	13	V1,V2	P	yes	C1	34	ND	M1	S3	7	0	12	5
CCM082	47	m	A1,A2,A3	15	V1	P	yes	C1	391	14	M1	S3	0	0	2	5
CCM083	50	m	A1,A2,A3,	13	V1	P	no	C1	U	60	M1,M2	S3	0	0	2	4
CCM085	29	f	A1,A6,A9	15	V1	P	yes	C1	190	50	M1	S3	0	0	2	5
CCM087	40	m	A1,A2,A3,	11	V1	P	no	C1	U	20	M1	S3	0	0	3	4
CCM091	32	m	A1,A6,A8,	14	V4	P	yes	C1	72	44	M1	S4	8	0	23	4
CCM095	34	f	A1,A4,A6	14	V1	P	no	C1	U	48	M1,M2	S3	0	0	3	3
CCM096	30	m	A4,A8	3	V1	P	yes	C1	28	60	M1,M2	S3	0	1	2	1
CCM097	35	m	A1,A4,A6,	14	V1	P	yes	C1	83	35	M1,M2	S3	0	0	4	5
CCM101	31	f	A1,A4,A6,	13	V1	P	yes	C1	264	42	M1	S3	0	0	2	4
CCM102	26	m	A1,A2,A6,	10	V1	P	no	C1	U	60	M1	S3	0	1	12	1
CCM103	36	m	A4,A8	11	V1	P	yes	C1	102	55	M1	S3	0	0	13	4
CCM104	22	m	A1,A4,A6	14	V1	P	yes	C1	32	50	M1,M2	S3	0	0	2	5
CCM108	18	m	A1,A6,A11	14	V1	P	yes	C1	49	55	M1,M2	S3	1	0	6	5
CCM109	26	f	A1,A4,A6	12	V1	P	yes	C1	61	50	M1,M2	S3	3	0	4	3
CCM111	28	m	A1,A4,A6,	12	V4	P	no	C1	543	50	M1,M2	S3	0	0	3	5