Routine Cranial CT before Lumbar Puncture in HIV positive adults presenting with Seizures at Mitchells Plain Hospital in Cape Town

by

Salma A Moolla

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Supervisors

1. Elma de Vries. Mitchells Plain Hospital and Division of Family Medicine, Faculty of Health Sciences, University of Cape Town.
2. Ashmitha Rajkumar. Department of Radiology, Mitchells Plain Hospital, Cape Town Metro District Health Services, Western Cape Government Health, South Africa.

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1. Preamble

1.1 Declaration

DECLARATION

I, Salma A. Molla, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Date: 26/02/2015

1.2 Abstract

Background

Current international guidelines recommend that a cranial computed tomography (CT) be performed, on all HIV positive patients presenting with new onset seizures, before a lumbar puncture (LP) is performed. In the South African setting, however, this delay could be life threatening. This study sought to measure the number of cranial CTs that contraindicate an LP and to predict which clinical signs and symptoms are likely to pose an increased risk from LP.

Methods

The study was performed at a district level hospital in the Western Cape. Data was collected retrospectively from October 2013 to October 2014. Associations between categorical variables were analysed using Pearson's Chi-squared test. Generalised linear regression was used to estimate prevalence ratios.

Results

100 out of 132 patients were studied. Brain shift contraindicated an LP in 5% of patients. Patients with brain shift presented with: decreased level of consciousness, focal signs, head ache and neck stiffness. 25% of patients had a space occupying lesion (defined as a discreet lesion that has a measurable volume) or cerebral oedema. Multivariate analysis showed a CD4 count < 50 (p=0.033) to be a statistically significant predictor of patients with a space occupying lesion (SOL) and cerebral oedema. Univariate analysis showed focal signs (p=0.0001), neck stiffness (p=0.05), vomiting (p=0.018) and a GCS<15 (0.002) to be predictors of SOL and cerebral oedema.

Conclusion

Patients with seizures in the HIV positive population have a high prevalence of SOLs and cerebral oedema but the majority of them are safe to LP.

Doctors can use clinical parameters to determine which patients can undergo immediate LP.

1.3 Acknowledgements

For their support during this project, I would like to thank my supervisor Elma de Vries for suggesting the dissertation topic, reading and responding timeously to multiple drafts and providing valued guidance throughout the process of developing this research. Thank you also to my co-supervisor Ashmitha Rajkumar for facilitating access to radiology reports and responding so proficiently to all my radiology questions.

Thank you to Mr Rauf Sayed for assisting me with the statistical analysis of the data. Thank you to Gavin van Wyk, specialist physician at Mitchells Plain hospital, for clarifying the medical queries arising from the folder review. Thank you to the records staff of Mitchells Plain hospital under the management of Daniel Vermeuelen for going beyond the call of duty to search for folders needed for the study. Thank you to researcher and friend Fathima Paruk for simplifying the data collation process.

Thank you to my family for the hours of quality time sacrificed towards achieving the completion of this dissertation.
And finally thank you to our nanny and helper, Nozanele Dayimani, the value of whom only a mother will understand.

1.4 List of Abbreviations

ABM: Acute Bacterial Meningitis

AIDS: Acquired Immune Deficiency Syndrome

CCM: Cryptococcol Meningitis

CD4: Cluster of Differentiation 4

CI: Confidence Interval

CLAT: Cryptococcal Latex Agglutination Test

CNS: Central Nervous System

CT: Computed Tomography

CSF: Cerebral Spinal Fluid

HIV: Human Immunodeficiency Virus

IV: Intravenous

LP: Lumbar Puncture

MmHg: Millimetres Mercury

MPH: Mitchells Plain Hospital

NHLS: National Health Laboratory Service

PR: Prevalence Ratio

SAMJ: South African Medical Journal

SOL: Space Occupying Lesion

TB: Tuberculosis

TBM: Tuberculosis Meningitis

UK: United Kingdom

US: United States

WHO: World Health Organisation

2. Literature Review

Routine Cranial CT before Lumbar Puncture in HIV positive adults presenting with Seizures at Mitchells Plain Hospital in Cape Town

2.1 Introduction

New onset seizures in HIV positive adults have been reported to have an incidence of around 6%[1]. Current guidelines, based on a number of international research articles [2,3,4,] , recommend that a cranial computed tomography (CT) be performed, on all HIV positive patients presenting with new onset seizures, before a lumbar puncture (LP) is performed. The cranial CT, in addition to being a diagnostic tool, is used to advise if an LP can be performed safely. The concern about performing LPs in this group is the risk of brain herniation secondary to raised intracranial pressure.

A prospective South African study performed at Chris Hani Baragwanath hospital found that 53.3% of HIV positive patients presenting with new-onset seizures had a space occupying lesion (SOL)[5]. A SOL is often misunderstood to always cause raised intracranial pressure. Van Crevel et al[3] has shown, however, that herniation from LP occurs when a SOL is accompanied by brain shift. Brain shift usually declares itself by clinical symptoms such as a decreased level of consciousness, headache and vomiting, neck stiffness, focal neurology, bradycardia and apnoea[3]. A focal neurological deficit can be defined as, 'a set of signs or symptoms in which causation can be localised to an anatomic site in the central nervous system'[6].

The incidence of brain shift in a patient presenting with seizures in an HIV positive adult is not known. In first world countries where CT scanners are readily available, it is feasible to CT scan all HIV positive individuals presenting with seizures soon after presentation. In many South African hospitals, however, there are no CT facilities on site and arranging a CT scan is time consuming and is often not done after hours. A working diagnosis and commencing treatment based on LP results can save time whilst waiting for a cranial CT.

The LP is essential to diagnose meningitis. Meningitis accounts for approximately 21.7% of causes of seizures in HIV positive South African adults[5]. Common causes for meningitis in our local setting are tuberculosis and cryptococcus. This could mean that if an LP is performed before a cranial CT, one in 5 patients will have a diagnosis before the cranial CT is performed. These patients will still need a cranial CT to exclude complications of the meningitis or a co-existing SOL, but appropriate treatment can be commenced if the LP results indicate a diagnosis.

2.2 Literature Search Strategy

The following search engines were used to find relevant articles; pubmed, google scholar and science direct. The terms entered were: '(lumbar puncture OR LP) AND (complications OR contraindications OR raised intracranial pressure OR risks OR cerebral herniation OR coning) AND (HIV OR seizures) NOT children, NOT babies, NOT adolescents. Other terms: '(CT head OR cranial CT or cranial computed tomography) AND (before) AND (LP OR lumbar puncture)'

2.3 Definition of raised intracranial pressure

Raised intracranial pressure can be defined in many ways. Roytowski[7] defines raised intracranial pressure, in the acute setting, as pressure within the cranial vault 'greater than 20-25mmHg for more than 5 minutes'[7]. The pressure can be measured using a manometer during lumbar puncture. The manometer is connected and read as soon as there is CSF backflow after the stylet is removed during lumbar puncture. It is essential that the patient be lying in a lateral position for accurate measurements.

Van Crevel[3] breaks down the definition of raised intracranial pressure to comprise a) raised CSF pressure and b) brain shift. Understanding these definitions is useful to understand the effect of LP on intracranial contents.

The cranial vault comprises three components: brain, cerebral spinal fluid (CSF) and blood[7]. The pressure within the cranial vault is, under normal circumstances, in equilibrium. This means that an increase in volume of a single component in the cranial vault will cause a decrease in volume of the other components with only a small increase in intracranial pressure, but only up to a point. This phenomenon is known as the Munro-Kellie doctrine. As intracranial pressure rises over a threshold, brain shifts occur[7]. Brain shift is important because it precludes brain herniation, which can be precipitated by lumbar punctures.

On the other hand, a raised CSF pressure without brain shift is occasionally an indication for LP. It is ironic that the lumbar puncture was introduced by Quincke to relieve the suffering of children with raised intracranial pressure from a communicating hydrocephalus[8]. It is well known that a lumbar puncture is thus safe and beneficial in some instances of raised intracranial pressure. In the South African setting, lumbar puncture and CSF drainage is commonly performed in patients with cryptococcal meningitis in an attempt to lower the raised intracranial pressure that accompanies the disease.

Although the above breakdown of the definition of raised intracranial pressure assists one to understand why lumbar punctures are sometimes contraindicated and sometimes beneficial in patients with raised intracranial pressure, Roytowski's[7] definition is more straight forward. He describes brain shift and brain ischemia as consequences of raised intracranial pressure and it seems that raised CSF pressure is synonymous with raised intracranial pressure in his definition.

Another cause for misunderstanding is the association of space occupying lesions or brain masses with raised intracranial pressure. A SOL is a cause of raised intracranial pressure but does not equate to raised intracranial pressure[3]. Other mechanisms of raised intracranial pressure are;
a) cerebral oedema (brain tissue)
b) vascular (congestive) brain swelling
c) hydrocephalus (CSF)[7].

There is enough evidence in the literature to show that there is reason to exercise caution when performing lumbar punctures when one suspects a patient to have a SOL[2,3,4]. It is important to accept though that not all patients with a SOL are unsafe to LP[4].

2.4 HIV, Seizures and Space occupying lesions

South Africa has one of the highest prevalence of HIV in the world. The HIV virus tends to frequently affect the central nervous system. In a South African study, Bhigjee[9] estimated that 70% of HIV individuals develop neurological complications. A retrospective study in Germany undertaken between 1992 and 2004 found that approximately 6% of 831 HIV positive individuals had seizures or epilepsy[1]. In comparison, the general population has an epilepsy prevalence of between 0.5 and 1%[9].There are multiple factors attributing to the increased incidence of seizures in the HIV positive population.

In the South African context, opportunistic infections account for a major cause of seizures in HIV positive individuals. These manifest as a SOL, a meningitis or an encephalomyelitis. Modi[5] reported that tuberculosis accounted for 64% of all opportunistic infections causing seizures at Baragwanath Hospital in Soweto. TB may present as meningitis or a SOL with a tuberculoma. The total prevalence of a SOL (53.3%) was more than twice that of meningitis (21.7%), confirming the high prevalence of SOL in this group of patients[5]. Other causes of opportunistic infections are cryptococcosis, toxoplasmosis, cysticercosis, syphilis and the herpes group of viruses.

Less common causes of seizures in the HIV positive population of South Africa are central nervous system (CNS) lymphomas, AIDS dementia complex and the HIV virus independently, especially during seroconversion[9]. Causes of seizures not directly linked to HIV may also occur such as metabolic abnormalities, alcohol abuse, prescribed or recreational drug induced seizures, cerebrovascular diseases, head injury and primary epilepsy[10].

2.5 Lumbar puncture and the Risk of Herniation

The risk of death as a direct result of an LP has been reported as early as 1896[11]. Since then multiple studies have been attempted to measure this risk. Before the advent of CT scanners, two studies, Lubic and Marotta(1954)[12] and Korein(1959)[13], both reported low incidences of clinical deterioration in patients following an LP . Lubic and Marotta concluded that out of 401 patients with a confirmed SOL (brain tumours) only one patient developed a complication after an LP was performed. This may be because slow growing lesions, such as brain tumours, will have a different pathophysiology when compared to acute lesions[3]. Acute lesions will generally tolerate less cerebral displacement and hence have a higher incidence of cerebral herniation[3]. Korein looked at a more varied group of 129 patients with raised CSF pressure and still found a less than 1% incidence of death following LP.

In 1969, however, Duffy[14], in a case series, described 30 patients with raised intracranial pressure who developed clinical deterioration within 12 hours after LP. All of these patients had one or more of the following; 'mental changes, progressive headache, focal neurology or papilloedema'. As this study was done in the pre-CT era, the author recommended the performance of a skull x-ray before LP in patients with suspected raised intracranial pressure to look for 'lateral displacement of a calcified pineal gland or definite erosion of the posterior clinoid processes' which would indicate cerebral mass lesions. Almost 50% of the patients in his study with clinical deterioration following LP showed the above mentioned skull x-ray changes[14].

With the advent of CT scanners in the 1970's clinicians began requesting CT scans before performing lumbar punctures on all patients with suspected meningitis, in order to rule out space occupying lesions[15]. A probable reason for this may have been the unreliance of 'papilloedema' to predict raised intracranial pressure[16]. In 1987 Gower et al[16] affirmed the superiority of cranial CT over papilloedema to predict safe LPs and outlined the CT

findings based on case reports that would contraindicate an LP. They concluded that ‘lateral shift of midline structures, loss of the suprachiasmatic and basilar cisterns, obliteration of the fourth ventricle, or obliteration of the superior cerebellar and quadrigeminal plate cisterns with sparing of the ambient cisterns’ are CT findings that should contraindicate an LP[16].

The increased use of CT before LP, however, has led to concerns such as, significant radiation exposure to patients from CT scans, fatal risk of delayed diagnosis and treatment of meningitis and to the wasteful expense on unnecessary CT scans. These concerns led Archer[2] to undertake a review of all articles, relating to CT before LP in acute meningitis, on Medline from 1965-1991. He found no evidence of any clinical deterioration from an LP in patients with ‘uncomplicated’ acute meningitis.

He did however make the recommendation that patients with the following do have a CT before LP[2]:

a) Unconsciousness
b) Focal findings
c) Papilloedema
d) Other atypical features (immune compromise, sinusitis, otitis media)

Despite Archer’s review in the Canadian Medical Association Journal in 1993, doctors continued to request CT scans prior to LP. This prompted Gopal et al[15] to conduct a prospective study published in 1999. His team attempted to correlate clinical predictors with patients at risk for LP before CT. 111 patients were assessed of which 2.7% had a CT which contraindicated an LP. Doctors who assessed this 2.7% (3 patients) correctly predicted that an LP would be unsafe for these patients. Gopal concluded that doctors’ clinical impression was the ‘strongest positive predictor of CT identified lesions contraindicating LP’. Other significant clinical predictors confirmed those of Archer’s review. Individual characteristics such as ‘immunosuppressed’ and ‘preceding seizures’ showed a positive correlation with new intracranial lesions but lacked statistical power. The need for a larger population study in these groups was recognised[14].

In the prospective Hasbun(2001)[4] study, conducted in the USA between 1995 and 1999, it was found that 76% of 301 patients with suspected meningitis underwent a cranial CT before a lumbar puncture[4]. Of the 76%, only two percent had contraindications to lumbar puncture on CT scan. These two percent (4 patients) had clinical signs of raised intracranial pressure before cranial CT and 1% (two patients) died secondary to raised intracranial pressure despite not having undergone an LP. Furthermore, 12 % of the patients had a space occupying lesion without a brain shift and they all underwent LP safely[4]. Still, Hasbun et al concluded that, due to the increased prevalence of an abnormality on cranial CT, patients with immunocompromise and patients with preceding seizures should have a preceding CT to rule out mass effect. This study became an important citation in international guidelines. It sought to limit the number of unnecessary CT scans performed in the West but here in South Africa where the HIV prevalence is so high, the number of CT scans indicated increased.

The significance of clinicians causing death from an LP and the way this fear affects medical practice led to a second review published by Van Crevel et al in 2002[3]. This time a Medline search was performed for articles related to the topic published between 1966 and 2001. The authors discussed reasons for the ongoing confusion and lack of clear guidelines for the practice of CT before LP. This is in part because of the lack of 'empirical evidence' and the unlikelihood of a randomised control trial being done on the topic. Van Crevel attempted to set out guidelines based on the pathophysiology of raised intracranial pressure that is known, but again as stated by the authors, these could only be 'offered in shades of grey'[3].

The common practice of requesting CT before LP was similar in the UK where a retrospective folder review conducted at the Horton General Hospital in 2004, found that 10% of all CT scans were carried out as a prelude to LP[17]. Of these, a third of scans were not mandatory according to the current guidelines at the time based on the 'Oxford textbook of medicine 2004' and the 'Saunders pocket essentials of clinical medicine'. The data analysis from this study led to the recommendation that any patient, with a normal

neurological examination and not suspected to have subarachnoid haemorrhage may have an immediate LP. This study was small, however (64 patients), and the immune status as well as seizure history of the patients were not described[17].

Beg et al (2007)[18] in a prospective study done in India, again attempted to identify a group of patients that will require CT before LP in suspected meningitis. The study comprised 108 patients of whom 29 patients had an abnormal CT. Based on a univariate regression analysis of patients' baseline characteristics, it was found that patients presenting with seizures had a significantly higher prevalence of an abnormal CT. It was thus recommended that all patients presenting with seizures have a CT before LP[18]. The number of patients who had an actual contraindication for an LP based on their CT results was, however, not mentioned.

It was in 2013 that Glimaker et al[19] published the third review article related to CT before LP. Relevant data from Medline was retrieved and analysed from 1965. Glimaker's team primarily focused on the risks of cerebral herniation from immediate LP versus the risk of delayed treatment from acute bacterial meningitis (ABM). In essence they found that the risk of death from delayed treatment in cases of ABM was significantly greater than the risk of herniation from an LP. This study led to the revised Swedish National Guideline for ABM. The most significant change in the guideline was the removal of immune compromised state, new onset seizures and decreased consciousness from the list of criteria that would contra indicate LP before CT. The omission was on the grounds that if the clinician strongly suspected an ABM in these patients, then it would be more appropriate to perform an immediate LP than to delay diagnosis and treatment of the meningitis. If the clinician felt that the diagnosis of a SOL is more probable than the diagnosis of meningitis, then it would be safer to perform a CT first.

New onset seizures and decreased consciousness are common presentations of ABM and space occupying lesions and therefore one has to consider other clues to the diagnosis. Although HIV is associated with a SOL,

if the patient presents with symptoms more suggestive of meningitis with no focal signs to suggest a SOL than an immediate LP would be indicated. These recommendations were based on hypothetical calculations of the risk of death based on the assumption that an LP will induce death in 1% of patients with a SOL and on the assumption that a 1 hour treatment delay in patients with ABM poses a relative increased mortality of 20%[19].

2.6 CT Scanners in South Africa

In September 2013, the SAMJ published an article titled 'The Kimberley hospital rule for urgent CT of the brain in a resource limited environment'[20]. The article expounded the fact that Kimberley Hospital is the only tertiary hospital in the Northern Cape and it serves approximately 1.4 million people. Furthermore Kimberley hospital has the only CT scanner in the province. This equates to 0.86 CT scanners per million population. In comparison, there were 29.4 CT scanners per million population in the USA in 2004[20]. Clearly, the indications for an urgent CT in developing countries like South Africa will need to be different.

Mitchells Plain Hospital (MPH) in the Western Cape opened its doors in July 2013 and its official opening was in November 2013. The hospital serves a population of approximately 440 000 people[21]. It provides a limited CT service and is equipped with a single CT scanner and a single radiologist. An after-hours CT service is unavailable. Patients requiring an immediate CT scan after hours must therefore be transferred to Groote Schuur hospital.

The estimated number of cranial CT's done in HIV positive patients due to seizures at Mitchells Plain hospital is unknown, as this information is not routinely recorded for statistical purposes. What can be estimated by the residing radiologist is that, on average 3-4 cranial CT's are done to diagnose the cause of seizures, on a daily basis. Mitchells Plain hospital has a large number of HIV positive patients, estimated to be a third of all medical admissions (personal communication with Dr. Gavin Van Wyk, Head of Medicine at MPH). It is therefore expected that a reasonable number of these

CT scans are done in HIV positive patients. The location of this study and hence a larger sample size of patients can provide new information about an at risk group of patients, regarding their safety of LP before CT.

2.7 Conclusion

Considering the lack of both international and local data that supports a blanket rule such as performing cranial CT's before LPs on all patients with HIV and seizures, and the discussed implications thereof, it is hoped that this study will make a significant contribution to clinical decision making. Our ultimate aim is to assess if the guidelines, that recommend a cranial CT before LP on all HIV positive patients presenting with seizures, are applicable to the HIV positive population of the Western Cape, South Africa.

2.8 References

1. Kellinghaus C, Enbring C, Kovac S, et al. Frequency of seizures and epilepsy in neurological HIV-infected patients. Seizure. 2007;17:27-33. [http://dx.doi.org/10.1016/j.seizure.2007.05.017]
2. Archer BD. Computed tomography before lumbar puncture in acute meningitis: a review of the risks and benefits. Can Med Assos J. 1993;146(6):961-965.
3. Van Crevel H, Hijdra A, De Gans J. Lumbar puncture and the risk of herniation: when should we perform CT? J Neurol. 2002;249:129-137. [http://dx.doi.org/10.1007/PL00007855]
4. Hasbun R, Abrahams J, Jekel J, et al. Computed tomography of the head before lumbar puncture in adults with suspected memingitis. N Eng J Med. 2001;345:1727-1733. [http://dx.doi.org/10.1056/NEJMoa010399]
5. Modi G, Modi M, Martinus I, et al. New onset seizures associated with HIV infection. Neurology. 2000;55:1558-1560. [http://dx.doi.org/10.1212/WNL.55.10.1558]
6. Wippold FJ, Cornelius RS, Aiken AH, et al. Focal neurological deficit. AJNR. 2008; 29: 1998-2000.
7. Roytowski D, Figaji A. Raised intracranial pressure: what it is and how to recognise it. CME. 2013;31(11):390-395.
8. Frederiks JA, Koehler PJ. The first lumbar puncture. J Hist Neurosci. 1997;6(2):147-53.
9. Bhigjee AI. Seizures in HIV/Aids: A Southern African Perspective. Acta Neurol Scand. 2005;112:4-7. [http://dx.doi.org/10.1111/j.1600-0404.2005.00500.x]
10. Garg RK. HIV infection and seizures. Postgrad Med J. 1999;75:387-390.
11. Lawrence RH. The role of lumbar puncture as a diagnostic tool in 2005. Critical Care and Resuscitation. 2005;7:213-220.
12. Lubick LG, Marotta JT. Brain tumour and lumbar puncture. Arch Neurol Psychiatry. 1958;72:568-572. Quoted by Van Crevel H, Hijdra A, De Gans J. Lumbar puncture and the risk of herniation: when should we perform CT? J Neurol. 2002;249:129-137

13. Korein J, Cravioto H, Leicach M. Reevaluation of lumbar puncture: a study of 129 patients with papilloedema or intracranial hypertension. Neurology. 1959;May(9):290-297. [http://dx.doi.org/10.1212/WNL.9.4.290] Quoted by Van Crevel H, Hijdra A, De Gans J. Lumbar puncture and the risk of herniation: when should we perform CT? J Neurol. 2002;249:129-137
14. Duffy GP. Lumbar puncture in the presence of raised intracranial pressure. Brit Med J. 1969;1:407-409. [http://dx.doi.org/10.1136/bmj.1.5641.407]
15. Gopal AK, Whitehouse JD, Simel DL et al. Cranial computed tomography before lumbar puncture, a prospective clinical evaluation. Arch Intern Med. 1999;159:2681-2685. http://dx.doi.org/10.1001/archinte.159.22.2681
16. Gower DJ, Baker AL, Bell WO, et al. Contraindications to lumbar puncture as defined by computed cranial tomography. Journal of Neurology, Neurosurgery, and Psychiatry. 1987;50:1071-1074. [http://dx.doi.org/10.1136/jnnp.50.8.1071]
17. Greig PR, Goroszeniuk D. Role of computed tomography before lumbar puncture: a survey of clinical practice. Postgrad Med J. 2006;82:162-165. [http://dx.doi.org/10.1136/pgmj.2005.041046]
18. Beg M, Ali S, Ahmad S, et al. A study of computed tomography of head before lumbar puncture in patients with suspected meningitis. JIACM. 2007;8(4): 355-359.
19. Glimaker M, Johansson B, Bell M, et al. Early lumbar puncture in adult bacterial meningitis-rationale for revised guidelines. Scandinavian Journal of Infectious Diseases 2013;45:657-663. [http://dx.doi.org/10.3109/00365548.2013.799289]
20. Bezuidenhout AF, Hurter D, Maydell AT, et al. The Kimberley Hospital Rule (KHR) for urgent computed tomography of the brain in a resource-limited environment.SAMJ.2013;103(9):646-651. [http://dx.doi.org/10.7196/samj.6876]
21. Western Cape Department of Health circular H28/2014, page 36.

3. Journal Manuscript

3.1 Cover Letter

Article Title:

Routine Cranial CT before lumbar puncture in HIV positive adults presenting with seizures at Mitchells Plain Hospital in Cape Town

Significance of work:

It is hoped that the results of the study will assist clinicians in making cost saving as well as lifesaving decisions in the management of their HIV positive patients who present with seizures.

It further hopes to provide doctors with useful information when they are required to make potentially risky diagnostic decisions when they encounter these patients in hospitals where CT scanners are unavailable.

Full Author Details:

1. Dr Salma Moolla; MB ChB; School of Public Health and Family Medicine, University of Cape Town, South Africa;

Contact Details:

Address: 202 Blenheim, 13 Bath road, Claremont, 7708

Email: samoolla@gmail.com

Tel no. 021 6830075

Cell no. 082 3496179

2. Dr Ashmitha Rajkumar; MB ChB, FC RAD (Diagnostic) (SA); Mitchells Plain Hospital, Cape Town Metro District Health Services, Western Cape Government Health, South Africa;

Contact Details:

Address: PO Box 782, Rondebosch, 7701

Email: Ashmitha.Rajkumar@westerncape.gov.za

Tel no. 021 6852286

Cell no. 083 4400573

3. Dr Elma de Vries; MB ChB, MFamMed, FCFP (SA);); Mitchells Plain Hospital, Cape Town Metro District Health Services, Western Cape Government Health, South Africa

Contact Details:

Address: 7 Hilton Road, Mowbray, 7700

Email: elma.devries@westerncape.gov.za

Tel no. 021 3774300

Cell no. 082 8286259

Corresponding Author:

Dr Salma Moolla (samoolla@gmail.com)

Author's Contributions:

1. Dr Salma Moolla – contributed the bulk of the data collection, collation and interpretation. Did the literature review and write up of the study.
2. Dr Ashmitha Rajkumar – contributed the interpretation of CT reports and general radiological concepts, provided the patients CT request forms for source patient identification and generally played a supportive and advisory role.
3. Dr Elma de Vries - Official supervisor of the research. Recommended the topic and assisted with the study methodology. Checked data and assisted with statistical conclusions. provided mentor role thoughout.

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Routine Cranial CT before lumbar puncture in HIV positive adults presenting with seizures at Mitchells Plain Hospital in Cape Town

SA Moolla[1], MB ChB; AK Rajkumar[2], MB ChB, FC RAD (Diagnostic) (SA); EM De Vries[1,2], MB ChB, MFamMed, FCFP (SA)

[1] School of Public Health and Family Medicine, University of Cape Town, South Africa
[2] Mitchells Plain Hospital, Cape Town Metro District Health Services, Western Cape Government Health, South Africa

Corresponding Author: SA Moolla (samoolla@gmail.com)

3.2 Abstract

Background
Current international guidelines recommend that a cranial computed tomography (CT) be performed, on all HIV positive patients presenting with new onset seizures, before a lumbar puncture (LP) is performed. In the South African setting, however, this delay could be life threatening. This study sought to measure the number of cranial CTs that contraindicate an LP and to predict which clinical signs and symptoms are likely to pose an increased risk from LP.

Methods
The study was performed at a district level hospital in the Western Cape. Data was collected retrospectively from October 2013 to October 2014. Associations between categorical variables were analysed using Pearson's Chi-squared test. Generalised linear regression was used to estimate prevalence ratios.

Results
100 out of 132 patients were studied. Brain shift contraindicated an LP in 5% of patients. Patients with brain shift presented with: decreased level of

consciousness, focal signs, head ache and neck stiffness. 25% of patients had a space occupying lesion (SOL), defined as a discreet lesion that has a measurable volume, or cerebral oedema. Multivariate analysis showed a CD4 count < 50 (p=0.033) to be a statistically significant predictor of patients with SOL and cerebral oedema. Univariate analysis showed focal signs (p=0.0001), neck stiffness (p=0.05), vomiting (p=0.018) and a GCS<15 (0.002) to be predictors of SOL and cerebral oedema.

Conclusion
Patients with seizures in the HIV positive population have a high prevalence of SOLs and cerebral oedema but the majority of them are safe to LP. Doctors can use clinical parameters to determine which patients can undergo immediate LP.

3.3 Introduction

New onset seizures in HIV positive adults have been reported to have an incidence of around 6%[1] . Current guidelines, based on a number of international research articles [2,3,4,], recommend that a cranial computed tomography (CT) be performed, on all HIV positive patients presenting with new onset seizures, before a lumbar puncture (LP) is performed. The cranial CT, in addition to being a diagnostic tool, is used to advise if an LP can be performed safely. The concern about performing an LP in this group is the risk of brain herniation secondary to raised intracranial pressure.

Raised intracranial pressure is defined, in the acute setting, as pressure within the cranial vault that is greater than 20-25mmHg for greater than five minutes (Roytowski)[5]. Raised intracranial pressure per se has not been conclusively linked to the risk of brain herniation from an LP and cannot be measured with a CT. An LP is in fact used to sometimes treat raised intracranial pressure such as in the case of idiopathic intracranial hypertension and cryptococcal meningitis.

Brain shift, however, has been associated with an increased risk of brain herniation from an LP and can be measured by a CT scan. The cranial CT can demonstrate hemispheral shift and gross generalised brain swelling, both contraindications to LP[6]. Brain shift occurs when differences in pressure between brain compartments, lead to brain compressing against certain intracranial structures[3]. The brain can get literally pushed to the point where it can herniate through the foramen magnum or the tentorial notch. Performing an LP, when there is brain shift, can further increase downward pressure and lead to fatal brain herniation[3]. Brain shift is usually caused by an expanding mass such as space occupying lesions, cerebral oedema and hydrocephalus[5].

A prospective South African study performed at Chris Hani Baragwanath hospital found that 53.3% of HIV positive patients presenting with new-onset seizures had a space occupying lesion (SOL)[7]. Many clinicians are of the opinion that a suspected SOL is an absolute contraindication to LP before CT. Van Crevel et al[3] has shown, however, that herniation from LP can only occur when a SOL is accompanied by brain shift. Brain shift usually declares itself by clinical symptoms such as a decreased level of consciousness, headache and vomiting, neck stiffness, focal neurology, bradycardia and apnoea[3]. The incidence of brain shift in a patient presenting with seizures in an HIV positive adult is not known.

In first world countries where CT scanners are readily available, it is feasible to CT scan all HIV positive individuals presenting with seizures soon after presentation. In many South African hospitals, arranging a CT scan is time consuming and is often not done after hours. A working diagnosis and commencing treatment based on LP results can save time and lives whilst waiting for a cranial CT.

The purpose of this study was to assess if current international guidelines that recommend a cranial CT before LP on all HIV positive patients presenting with seizures, is applicable to the HIV positive population of the Western Cape, South Africa.

3.4 Methods

This was a cross sectional, observational study conducted at Mitchells Plain Hospital (MPH) from October 2013 to October 2014. The study population comprised HIV positive patients with seizures, presenting for cranial CT. The CT request forms filed in the radiology department at MPH were used to identify patients to be included in the study. Initially, a broad manual search for any patient whose cranial CT was requested for seizures, was undertaken. The search was then streamlined to only include HIV positive patients and seizures. Where there was doubt regarding the HIV status, confirmation was sought via the National Health Laboratory (NHLS) database. Patients under the age of 18 and patients, whose seizures were acutely trauma related, were excluded from the study.

Data was extracted onto a data collection sheet from patient folders, the NHLS database and the radiology database where necessary. Patients' demographic details, CD4 count, risk factors for seizures, seizure history, symptoms and signs of brain shift on presentation, CT information, LP findings, final diagnoses and prognoses were recorded. Criteria used for CT findings that would contraindicate and LP included any midline shift of the midline structures, effacement of any of the basal cisterns and obliteration of the fourth ventricle. Diagnoses were the most likely diagnosis for the patient, recorded in the notes. This was not necessarily based on organism detection but also on doctors' clinical impressions. Focal signs were regarded as present if there were any signs or symptoms that could localise pathology to an anatomic site in the central nervous system.

The data was then captured onto a spreadsheet in *Microsoft Excel* and was analysed using STATA 13.0 (*StataCorp. 2013)*. Associations between categorical variables were analysed using Pearson's Chi-squared test and prevalence ratios (PRs) with 95 per cent confidence intervals. Variables that were considered as potential risk factors, such as age, gender, CD4, seizure history, type of fit and signs and symptoms of brain shift, were included in the model for generalized linear regression analysis to estimate the prevalence

ratio (PR). For all analyses, a P-value of less than 0.05 and a 95% confidence interval that did not span unity were considered the thresholds of statistical significance.

Ethical approval was obtained from the UCT research ethics committee and the Western Cape Provincial Health Research Committee granted permission to conduct the study. Patients' identities were protected as their names were not recorded.

3.5 Results

A total of 132 CT request forms, in the period October 2013-October 2014, identified suitable patients to be included in the study. This suggests a minimum of 11 cranial CT's performed monthly, at MPH, in HIV positive patients, presenting with seizures. The first 100 patients whose folders were accessed were studied.

Table 1. Baseline characteristics of patients

Age: Median	38 years
Average	39 years
IQR	32-45 years
	n
CD4 Count: <50	20
50-200	23
200-350	24
>350	32
Unknown	1
Risk Factors for Seizures: Systemic illness	38
Alcohol/Substance use	21
History of head injury	13
Abnormal chemistry	8
Seizure History: New onset seizure	81
Known epileptic	19
Type of Seizure: Generalised	74
Focal	16
Undocumented	10

Clinical signs and symptoms suggestive of brain shift:	
Headache	21
Vomiting	4
Visual disturbances	1
GCS<15	38
Focal signs	11
Neck stiffness	10
Papilloedema	None documented
IQR= interquartile range, *n* = portion of total sample (N=100) GCS= Glascow Coma Scale	

Baseline characteristics of patients are presented in table 1. Patients' ages ranged from 21-73, with the median age being 38. 20 percent of patients had advanced immunosuppression with a CD4 count of less than 50. Patients who presented with seizures usually had some form of systemic illness such as TB or Gastroenteritis –with- renal- impairment, which also placed them at risk for metabolic abnormalities, and hence seizures. New onset, generalised seizures were commonest. There were 42 percent of patients who were asymptomatic at the time of presentation. Headache and a decreased level of consciousness were the most frequent clinical presentations. The presence or absence of papilloedema was recorded in 1 of 100 folders. The assumption is that papilloedema was not checked for in the remaining 99 patients.

Table 2. Description of patients with brain shift

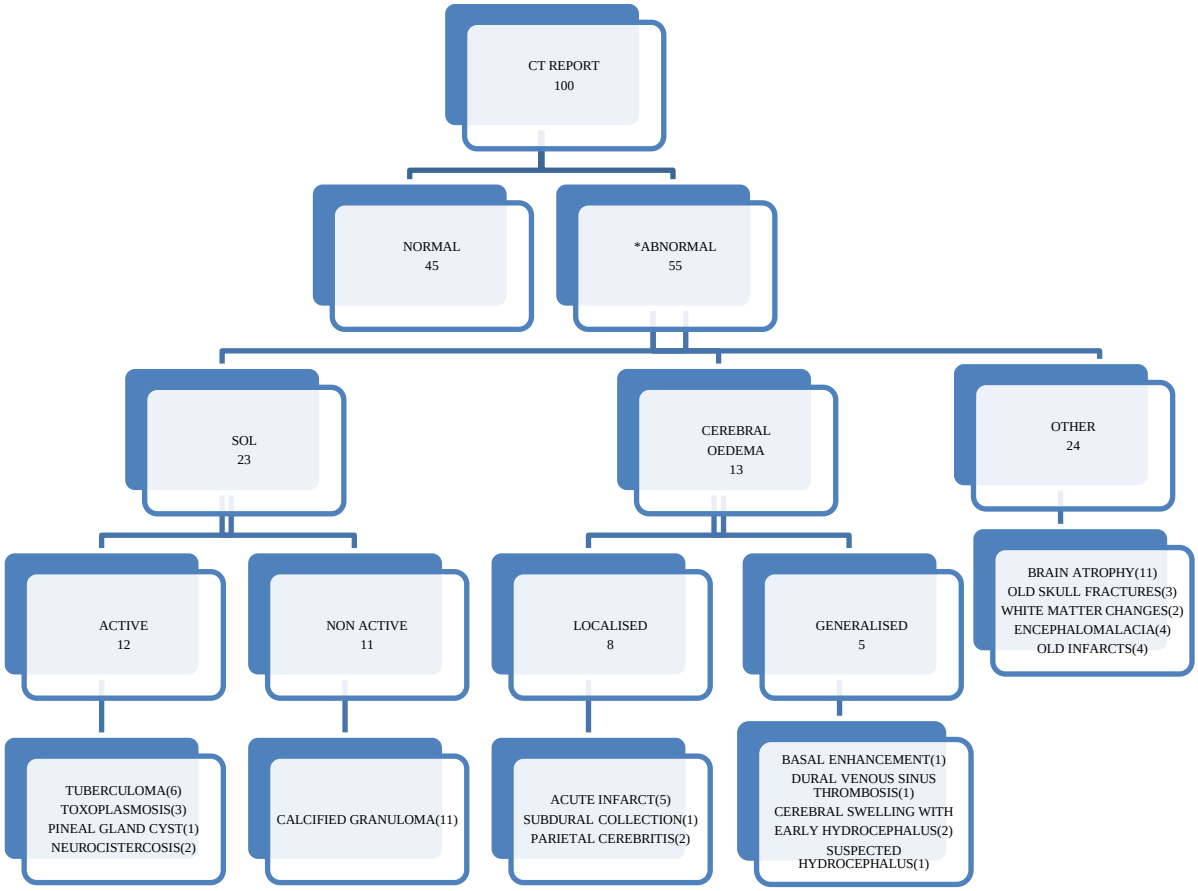
	CD4 count	Gender	Type of seizure	Symptoms	CT Finding	LP Done	Adverse effect from LP	Diagnosis	Prognosis
1	<50	Male	Generalised	Focal signs Impaired consciousness GCS14	Active space occupying lesion	No	Not applicable	Toxoplasmosis	Referred Tertiary Institution
2	50-200	Female	Focal	Focal signs Headache GCS15	Active space occupying lesion	No	Not applicable	Toxoplasmosis	Recovery and discharge
3	50-200	Female	Unrecorded	Impaired consciousness GCS13	Generalised cerebral oedema	Yes, after second scan	No	Meningitis bacterial/TB	Recovery and discharge
4	200-350	Male	Generalised	Impaired consciousness Neck stiffness GCS not documented	Active space occupying lesion	Yes, before scan	No	Tuberculoma/ TB Meningitis	Recovery and discharge
5	200-350	Female	Generalised	Impaired consciousness GCS14	Localised cerebral oedema	No	Not applicable	Chronic haematoma/ empyema	Referred Tertiary Institution

Brain shift was seen on CT scan in 5 percent of the patients. Details of these patients are given in table 2. All of these patients had one or more signs and symptoms of raised intracranial pressure/brain shift on presentation. One patient with suspected meningitis had an LP before the cranial CT, which showed brain shift. No adverse effects were reported from the LP.

Results of cranial CTs are described in figure 1. More than half of the patients had an abnormal cranial CT. Many of these abnormalities were old and untreatable. The patients with active SOLs, together with the patients with cerebral oedema (generalised and localised) were at risk for developing brain shift. This comprised 25 percent of the study population. Calcified granulomas were categorised into inactive SOL as they have no potential for growth and expansion. In our setting a calcified granuloma is attributed to old TB but it has a number of different causes. Nearly a quarter (24 percent) of patients had brain abnormalities that may have explained patients' seizures,

but were incurable such as old infarcts, calcified granulomas and focal encephalomalacia.

Figure 1. Description of CT scans



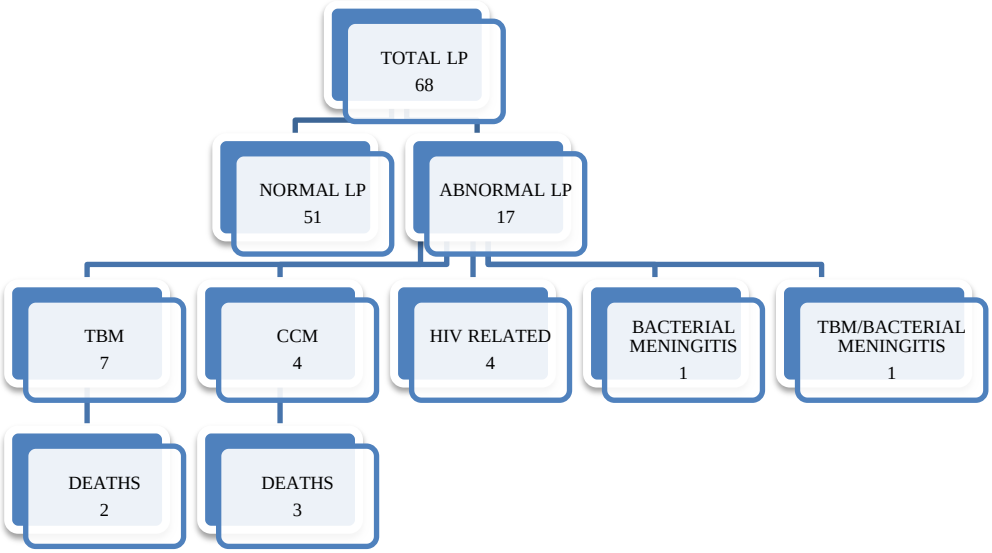
Generalised linear regression was used to predict patients with SOL/cerebral oedema (table 3). Associations were initially found in the following categories; age, CD4 count, asymptomatic, focal signs, neck stiffness, vomiting and decreased level of consciousness. However, after multivariate analysis only a CD4 count less than 50, was associated with an increased risk for SOL/cerebral oedema. All other variables such as age, gender, history of seizure, type of seizure (whether localised or generalised) had no predictive value of at risk patients. The group of patients with brain shift was too small to show any significant clinical predictors and they were thus grouped together with the patients with active SOLs and cerebral oedema.

Table 3. Univariate and multivariate analyses of potential predictors of patients with active SOL and cerebral oedema

Potential predictors of at risk patients	Univariate						Multivariate		
	Total number of patients	Percentage of patients with active SOL or cerebral oedema	PR	95% CI	P-value		PR	95% CI	P-value
Age: <40	58	32.8	2.3	1.0 – 5.2	0.0352		1.8	0.7 – 4.5	0.236
CD4 >350	32	3.1	1				1		
200-350	24	25.0	2.3	1.4 – 3.8	0.0143		8.3	1.0 – 71.0	0.053
50-199	23	34.8	2.7	1.7 – 4.4	0.0017		7.5	0.9 – 62.0	0.063
<50	20	50.0	3.7	2.1 – 6.6	0.0001		10.1	1.2 – 85.4	0.033
Clinical Presentation									
Asymptomatic	44	6.8	0.2	0.1 – 0.5	0.0002		0.3	0.1 – 1.3	0.118
Focal Signs	11	72.7	3.8	2.2 – 6.7	0.0001		2.0	0.8 – 5.1	0.154
Neck stiffness	10	50.0	2.3	1.1 – 4.7	0.0543		1.0	0.4 – 2.8	0.995
Vomiting	4	75.0	3.3	1.7 – 6.4	0.0184		1.5	0.4 – 6.2	0.586
GCS<15	38	42.1	2.9	1.4 – 5.9	0.0020		1.0	0.4 – 2.7	0.984
PR= Prevalence ratio, CI= Confidence Interval, GCS= Glascow Coma Scale									

Lumbar punctures were performed in 68 percent of patients presenting with seizures. Despite international guidelines, 52 percent of these patients had an LP before cranial CT, with no adverse effects reported. A markedly abnormal CSF result was found in 24 percent of patients who underwent LP, of which 75 percent was diagnosed with infective meningitis (figure2). Meningitis comprised more than half of the total study mortality (5 out of 9 deaths). Other causes of death were from renal failure (2 out of 9 deaths) and gastroenteritis (2 out of 9 deaths).

Figure 2. Description of LP results



The portion of patients who did not have a clear diagnosis on discharge comprised 23 percent (n=23), 13 of whom had an LP and 10 of whom did not have an LP.16 percent of patients had seizures attributed to drugs, alcohol, a previous head injury, a metabolic cause or breakthrough seizures (in the known epileptic group).

3.6 Discussion

Uptodate[8], the international evidence-based clinical decision support resource, has advised that patients with a suspected meningitis be scanned first if they have any of the following: decreased level of consciousness, focal signs, papilloedema, preceding seizures and impaired cellular immunity. This recommendation was based on the study by Hasbun et al (2001)[4]. By strict international standards all patients in this study ought to have had a CT before LP. Our study sought to measure the risk of LP in patients with preceding seizures and impaired cellular immunity by measuring the number of CT scans that reported brain shift and hence contraindicated an LP. It is the first study done to look at the prevalence of brain shift and patients at risk for brain shift (SOL/cerebral oedema) in this particular subset of patients. An

attempt was also made to predict if clinical factors in this group could be used to decide which patients needed a preceding cranial CT.

Despite the expected increased prevalence of an active SOL (12%) and cerebral oedema (13%) in the population studied, the actual number of patients who had a contraindication to LP on CT scan was small (5%). This prevented us from drawing any significant statistical conclusion from the descriptive results in diagram 1. We were however able to show statistically significant associations, on univariate analysis, between clinical predictors and patients with an active SOL or cerebral oedema. Active SOLs and cerebral oedema are disease processes that could lead to brain shift. It can thus be safely assumed that patients with no clinical predictors of SOL and cerebral oedema will have a reduced probability of brain shift.

The study confirmed recommendations that a decreased level of consciousness and focal signs are significant predictors of patients at risk for brain shift. It also found that in HIV positive patients with preceding seizures, vomiting and neck stiffness may also be predictors of SOL/cerebral oedema. Of significance is the finding on multivariate analysis that shows that a CD4 count of less than 50 is associated with increased risk for SOL/cerebral oedema. A CD4 count of less than 50 is a specific predictor and should be given more weight in clinical decision making. Two asymptomatic patients, with a CD4 less than 50, underwent an LP and subsequently had an active SOL on cranial CT. It must be stressed, however, that none of the asymptomatic patients were unsafe to LP.

Papilloedema has been described as a contraindication to LP. The patients in our study were almost entirely not examined for papilloedema. This may be due to the fact that it is often difficult to perform an ophthalmoscopy in a bright and busy emergency room, especially when doctors' experience with ophthalmology is limited. Papilloedema, however, is a late finding of raised intracranial pressure, and guidelines from Queens University recommend performing an LP even when the optic discs cannot be visualised[9], if there are no other contraindications to performing an LP.

Extensive research was performed by the Swedish Infectious Disease Society regarding the comparative risk between immediate LP before CT and the risk of delayed LP (and inevitably delayed treatment) in adults with suspected acute bacterial meningitis. Hypothetical calculations of these risks, in different clinical settings with varying probabilities of cerebral mass lesions and acute bacterial meningitis (ABM), were presented. The authors worked on the premise that although there is little evidence of an association between LP and brain herniation in acute bacterial meningitis; there is sufficient evidence of an association between LP and brain herniation in patients with cerebral mass lesions. The risk of brain herniation, associated with lumbar punctures, in patients with cerebral mass lesions, however is small and was assumed to be between 1-2%. It was concluded that where a patient had no clinical signs to indicate a SOL, an immediate LP will be advantageous. This would apply even where the probability of ABM is more than 0.5%. This research has led to the revised Swedish recommendation for early lumbar puncture in 2009, which removed impaired immunity and new onset seizures as indications for a preceding cranial CT[10].

Interestingly, Martin Glimaker and his team recently investigated the outcome of the 2009 recommendations. A total of 318 patients seen between 2010 and 2012 (after the revised Swedish guidelines) were compared to 394 patients seen between 2004 and 2009. They found that 57% of patients with suspected meningitis had a CT before LP between 2010 and 2012. The patients who had an immediate LP showed a lower incidence of mortality and sequaelae compared to those who had a CT before LP. The two groups were similar with regard to age and level of consciousness. They concluded that the 2009 recommendations, that removed decreased level of consciousness as an indication for CT before LP, is associated with improved outcome and that 'revision of international guidelines should be considered'[11].

An American study by O'Laughlin et al (2013)[12] examined 1737 CT reports in various patients with both medical and trauma related presentations, to assess the prevalence of CT scans that contraindicate LPs. It was found that 14.6% had one or more high risk findings that would contraindicate LP,

compared to our study where 5% of CT scans contraindicated an LP. The study also found no clinical correlation between clinical presentation and CT findings. It did, however, draw the conclusion that since brain herniation precipitates death, radiologists are becoming increasingly cautious when reporting on CT scans. This assumption is made because actual brain herniation from LP is very rare. There have been reports from casualty staff at MPH of patients undergoing an LP before CT which later reported that an LP is contraindicated. These patients, like the one reported in this study, had no adverse event after the preceding LP.

Cranial CT provided a diagnosis for seizures in more than 50% of our patients and it should remain an important diagnostic tool in our population. What is questionable is the need to provide our patients with urgent cranial CT's in order to rule out brain shifts before lumbar punctures. There are substantial financial and clinical implications that arise from this recommendation. The Hasbun study (2001)[4] reported a 2 hour time delay to lumbar puncture and longer emergency department stays when patients underwent cranial CT before LP. In our setting the time delays would be much longer especially after hours when there is no CT service on site. The shortage of CT scanners and a lack of funding for staff has led to studies such as, 'The Kimberley hospital rule for urgent CT of the brain in a resource limited environment'[13] and 'Appropriateness of computed tomography and magnetic resonance imaging scans in the Eden and Central Karoo districts of the Western Cape Province, South Africa'[14]. These studies like ours highlight the need to implement local, cost effective CT guidelines.

Apart from the financial implications of arranging urgent CT scans, there is the clinical consideration. The highest number of deaths in our study was from CCM (3 out of 9 deaths), followed by TBM (2 out of 9 deaths). The high case fatality rate in CCM, predicted by the WHO to be between 35-65% in Sub-Saharan Africa prompted the recommendation that patients with a CD4 less than 100 have early screening for the disease[15]. Lumbar puncture and CSF analysis remain the key diagnostic test for CCM but if an LP needs to be delayed then an urgent serum cryptococcal latex antigen test (CLAT) must

be performed on all patients suspected of CCM[16]. Patients with cryptococcal meningitis often present with a severe headache and an isolated sixth nerve palsy. The presentation of the sixth nerve palsy will not be a contraindication to lumbar puncture according to the guideline in 'The South African Journal of Epidemiology and Infections (SAJEI)'[6]. Here it states that isolated cranial nerve palsies are excluded from the focal signs which generally contraindicate an LP.

Current guidelines recommend blood culture analysis and IV antibiotics in cases of suspected meningitis where an LP is contraindicated[6]. The administration of IV antibiotics is intended to ensure that patients with bacterial meningitis are not deprived of emergency lifesaving treatment whilst waiting for lumbar puncture results. The prevalence of bacterial meningitis in our study was low in comparison to TBM and CCM. This is not unusual, as the causes of meningitis in a population with a high prevalence of TB and HIV, similar to our own, has already been described. The LP results of 4549 patients were studied between 2006 and 2008 at GF Jooste hospital in the Western Cape and CCM followed by TBM were the most common causes of meningitis in this setting[17]. Delayed lumbar puncture will delay treatment in these patients and worsen their outcome.

3.7 Limitations

The most significant limitation of this study was the sampling strategy. Ideally, to measure the number of people who suffered immediate death after LP, it would have been necessary to identify all patients who had an LP. By identifying patients from their CT request forms, the study overlooked a possible group of patients who may have suffered immediate cerebral herniation post LP and never survived to have had a CT. Consultation with the Head of Casualty however revealed, that no patient to his knowledge, experienced cerebral herniation from an LP at MPH (personal communication Dr. Kamil Vallabh). Furthermore, at least 50% of our patients did have an LP before CT and had no reported complications.

The study design was adequate to report on the number of CT scans where an LP was contraindicated. The small study sample and the small percentage of patients with brain shift, prevented us from predicting any statistically relevant factors for brain shift. Enough information was available to describe these patients and it is not unreasonable to conclude that any decreased level in consciousness or focal signs should contraindicate an LP before CT in patients with HIV and seizures.

Another limitation is that our research conclusions are based on doctors' clinical impressions and not necessarily measurable information. Neck stiffness, for example is a subjective clinical finding and should not be used in isolation to decide on management steps. Similarly, patient diagnoses were not based on hard facts, due to the low detection of organisms on CSF microscopy and culture as well as the absence of histology on SOLs. In such cases doctors used their clinical judgement as well as evidence of disease elsewhere to make a diagnosis and start treatment. Cryptococcal meningitis and toxoplasmosis were however definitive diagnoses, based on positive india ink staining or cryptococcal antigen testing and positive toxoplasmosis serology respectively.

This was a retrospective folder review and all CT scans were reported by the same radiologist. It would have been more reliable if the scans were seen by two radiologists, as this would have reduced any interpretation bias.

3.8 Conclusion

Patients with seizures in the HIV positive population have a high prevalence of SOLs and cerebral oedema but the majority of them are safe to LP. Indicators such as a decreased level of consciousness, focal signs, vomiting, neck stiffness and a CD4 count of less than 50 should alert doctors to the possibility of at risk patients. All of the asymptomatic patients were safe to LP but should still undergo non urgent cranial CT due to the limited occurrence of SOL and cerebral oedema in this group (6.8%). Cryptococcal meningitis accounted for the highest mortality and doctors need to be more vigilant in

performing serum CLATs if the LP is delayed, following up on results promptly to make earlier diagnoses and starting treatment sooner. There were no adverse events reported after any of the LPs performed on the patients in this study.

3.9 References

1. Kellinghaus C, Enbring C, Kovac S, et al. Frequency of seizures and epilepsy in neurological HIV-infected patients. Seizure 2007;17:27-33. [http://dx.doi.org/10.1016/j.seizure.2007.05.017]
2. Gopal AK, Whitehouse JD, Simel DL, et al. Cranial Computed Tomography Before Lumbar Puncture, A Prospective Clinical Evaluation . Arch Intern Med 1999;159:2681-2685. [http://dx.doi.org/10.1001/archinte.159.22.2681]
3. Van Crevel H, Hijdra A, De Gans J. Lumbar puncture and the risk of herniation: when should we perform CT? J Neurol 2002;249:129-137. [http://dx.doi.org/10.1007/PL00007855]
4. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. N Eng J Med 2001;345:1727-1733. [http://dx.doi.org/10.1056/NEJMoa010399]
5. Roytowski D, Figaji A. Raised intracranial pressure: what it is and how to recognise it. CME 2013;31(11):390-395.
6. Boyles TH, Bamford C, Bateman K et al. Guidelines for the Management of acute meningitis in children and adults in South Africa. South Afr J Epidemiol Infect 2013;28(1):5-15
7. Modi G, Modi M, Martinus I, Saffer D. New onset seizures associated with HIV infection. Neurology 2000;55:1558-1560.[http://dx.doi.org/10.1212/WNL.55.10.1558]
8. Johnson KS, Sexton DJ. Lumbar puncture: Technique, indications, contraindications, and complications in adults. Uptodate 2013. http://www.uptodate.com/contents/lumbar-puncture-technique-indications-contraindications-and-complications-in-adults#H7 (accessed 14 November 2014)
9. Queens's University School of Medicine. Lumbar Puncture. meds.queensu.ca/central/assets/modules/lumbar_puncture/to_ct_or_not_to_ct_ that_is_the_question.html (accessed 14 November 2014)

10. Glimaker M, Johansson B, Bell M, et al. Early lumbar puncture in adult bacterial meningitis-rationale for revise guidelines. Scandinavian Journal of Infectious Diseases 2013;45:657-663. [http://dx.doi.org/10.3109/00365548.2013.799289]
11. Glimaker M, Johansson B, Grindborg O, et al. Adult Bacterial Meningitis: Earlier Treatment and Improved Outcome Following Guideline Revision Promoting Prompt Lumbar Puncture. Clinical Infectious Diseases 2015;60(8):1162–9. [DOI: 10.1093/cid/civ011]
12. O'Laughlin KN, Hoffman JR, Go S, et al. Nonconcordance between Clinical and Head CT Findings: The Specter of Overdiagnosis. Emergency Medicine International 2013;Article ID 314948, 7 [http://dx.doi.org/10.1155/2013/314948]
13. Bezuidenhout AF, Hurter D, Maydell AT, Van Niekerk F, De Figueiredo SAB, et al. The Kimberley Hospital Rule (KHR) for urgent computed tomography of the brain in a resource-limited environment. SAMJ 2013;103(9):646-65 [http://dx.doi.org/10.7196/samj.6876]
14. Becker J, Jenkins LS, de Swardt M, et al. Appropriateness of computed tomography and magnetic resonance imaging scans in the Eden and Central Karoo districts of the Western Cape Province, South Africa. SAMJ 2014;104(11):762-765. [http://dx.doi.org/10.7196/samj.8158]
15. World Health Organization. Rapid Advice: Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-infected Adults, Adolescents and Children. Geneva: World Health Organization, 2011. http://www.who.int/hiv/pub/cryptococcal_disease2011/en/ (accessed 10 December 2014)
16. Govender NP, Meintjes, Bicanic T, et al. Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update. SAJHIVMED 2013;14(2):76-86
17. Jarvis N, Meintjes G, Williams A, et al. Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspected cases. BMC Infectious Diseases 2010;10:67 [http://dx.doi.org/10.1186/1471-2334-10-67]

4. Appendix

4.1 Ethics approval letter

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences

Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492 • **Facsimile** [021] 406 6411
Email: Sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

05 June 2014

HREC/REF: 289/2014

Dr E de Vries
Public Health & Family Medicine
Entrance 5, Level 2
Falmouth Building
FHS

Dear Dr de Vries

Project Title: ROUTINE: CRANIAL CT BEFORE LUMBAR PUNCTURE IN HIV POSITIVE ADULTS PRESENTING WITH SEIZURES AT MITCHELLS PLAIN HOSPITAL IN CAPE TOWN-(MMed-candidate-Dr S Moolla)

Thank you for your letter dated 19 May 2014, addressing the issues raised by the Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year until the 30 June 2015.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

We acknowledge that the following student:- Dr Salma Moolla is also involved in this project.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Hrec/ref:289/2014

4.2 Data collection sheet

Folder number	
CD4 Count	

Demographic Characteristics

1. SEX	M	f
2. AGE		
3. AREA OF RESIDENCE		

Risk Factors for Seizures

1.alcohol/ drugs	
2.history head injury	
3.abnormal chemistry	
4.family history of epilepsy	
5.systemic illness	
6. none known	
7.none documented	
8.other	

Seizure History

1. history of seizure	first onset seizures	known epileptic
2. witnessed: medical staff		
: non medical staff		
3. type of fit: generalised		
: focal		
: unrecorded		

Symptoms on presentation suggestive of raised intracranial pressure

1.headache	
2.vomiting	
3.visual disturbances	
4.decreased level of consciousness	
5.focal signs	
6.papilloedema	
7.meningism	
8.other	

GCS:

CT Information

1. Space occupying lesion: yes
: no

2. Brain Shift present : yes
: no

3. Was patient booked via | Casualty | opd | Ward

4. Other CT findings | Atrophy | basal enhancement | | haemorrhage |

LP Findings

1. Was LP done: Yes
: no
normal
reason

2. Was LP done : before CT scan
: after CT scan

3. Were there adverse events recorded due to LP :yes
: no
describe

Final Diagnosis

1.TB Meningitis
2.Tuberculoma
3.Toxoplasmosis
4.Cysticercosis
5.Lymphoma
6.Cryptococcus
7.Syphylis
8.Drug/Alcohol
9. Inherited
10.Previous head injury
11.Metabolic causes
10. Other
Specify

Prognosis

1. recovery and discharge
2. Death within 12 hours of LP
3. Death after 12 hours of LP or no LP

4.3 List of Tables:

4.3.1 Table 1. Baseline characteristics of patients

Age: Median	38 years
Average	39 years
IQR	32-45 years
	n
CD4 Count: <50	20
50-200	23
200-350	24
>350	32
Unknown	1
Risk Factors for Seizures: Systemic illness	38
Alcohol/Substance	21
History of head injury	13
Abnormal chemistry	8
Seizure History: New onset seizure	81
Known epileptic	19
Type of Seizure: Generalised	74
Focal	16
Undocumented	10
Clinical signs and symptoms suggestive of brain shift:	
Headache	21
Vomiting	4
Visual disturbances	1
GCS<15	38
Focal signs	11
Neck stiffness	10
Papilloedema	None documented
IQR= interquartile range, *n*= portion of total sample (N=100) , GCS= Glascow Coma Scale	

4.3.2 Table 2. Description of patients with brain shift

	CD4 count	Gender	Type of seizure	Symptoms	CT Finding	LP Done	Adverse effect from LP	Diagnosis	Prognosis
1	<50	Male	Generalised	Focal signs Impaired consciousness GCS14	Active space occupying lesion	No	Not applicable	Toxoplasmosis	Referred Tertiary Institution
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3	50-200	Female	Unrecorded	Impaired consciousness GCS13	Generalised cerebral oedema	Yes, after second scan	No	Meningitis bacterial/TB	Recovery and discharge
4	200-350	Male	Generalised	Impaired consciousness Neck stiffness GCS not documented	Active space occupying lesion	Yes, before scan	No	Tuberculoma/ TB Meningitis	Recovery and discharge
5	200-350	Female	Generalised	Impaired consciousness GCS14	Localised cerebral oedema	No	Not applicable	Chronic haematoma/ empyema	Referred Tertiary Institution

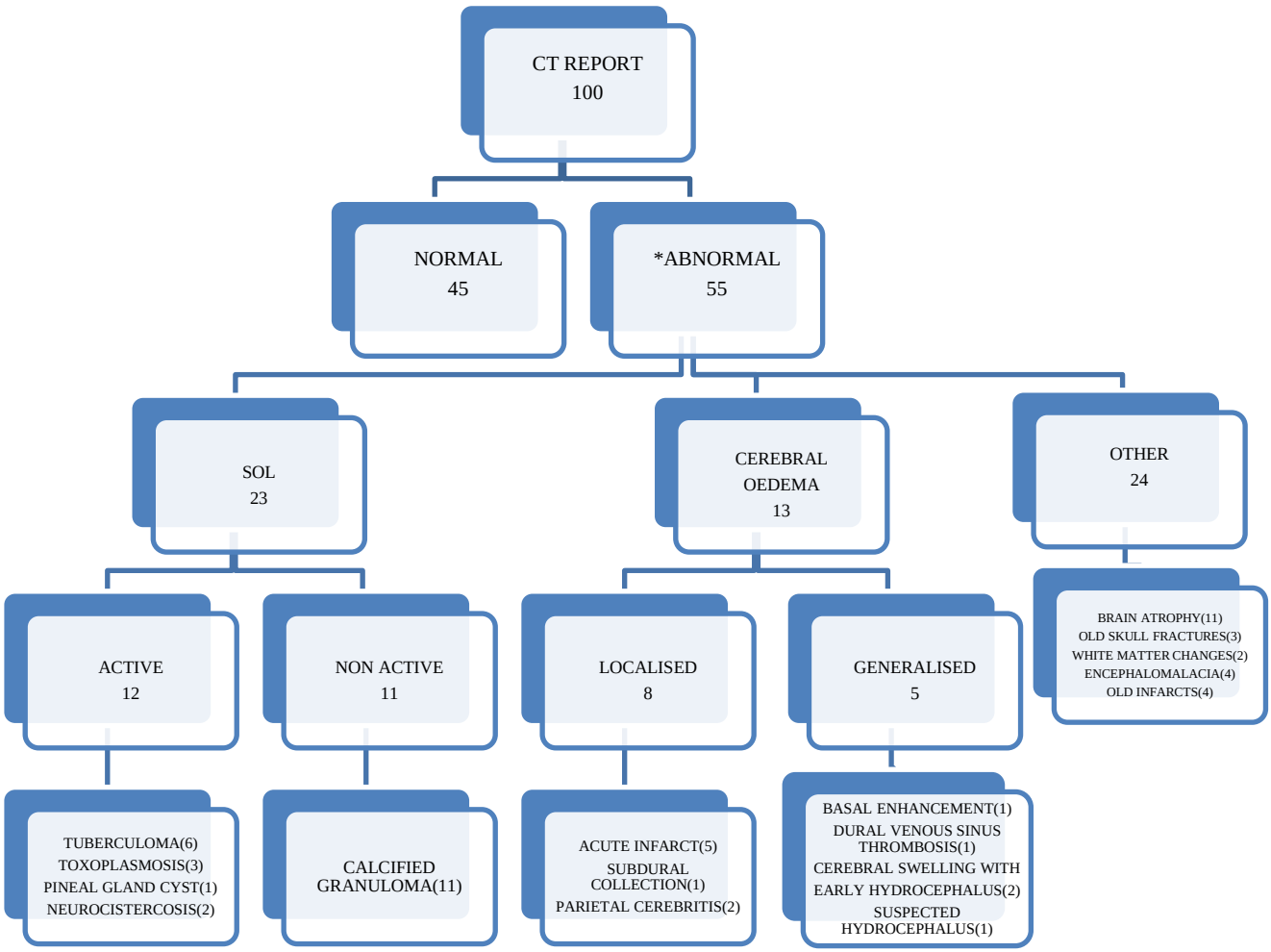
4.3.3 Table 3. Potential predictors of patients with active SOL and cerebral oedema

Potential predictors of at risk patients	Univariate						Multivariate		
	Total number of patients	Percentage of patients with active SOL or cerebral oedema	PR	95% CI	P-value		PR	95% CI	P-value
Age: <40	58	32.8	2.3	1.0 – 5.2	0.0352		1.8	0.7 – 4.5	0.236
CD4 >350	32	3.1	1				1		
200-350	24	25.0	2.3	1.4 – 3.8	0.0143		8.3	1.0 – 71.0	0.053
50-199	23	34.8	2.7	1.7 – 4.4	0.0017		7.5	0.9 – 62.0	0.063
<50	20	50.0	3.7	2.1 – 6.6	0.0001		10.1	1.2 – 85.4	0.033
Clinical Presentation									
Asymptomatic	44	6.8	0.2	0.1 – 0.5	0.0002		0.3	0.1 – 1.3	0.118
Focal Signs	11	72.7	3.8	2.2 – 6.7	0.0001		2.0	0.8 – 5.1	0.154
Neck stiffness	10	50.0	2.3	1.1 – 4.7	0.0543		1.0	0.4 – 2.8	0.995
Vomiting	4	75.0	3.3	1.7 – 6.4	0.0184		1.5	0.4 – 6.2	0.586
GCS<15	38	42.1	2.9	1.4 – 5.9	0.0020		1.0	0.4 – 2.7	0.984

PR= Prevalence ratio, CI= Confidence Interval, GCS= Glascow Coma Scale

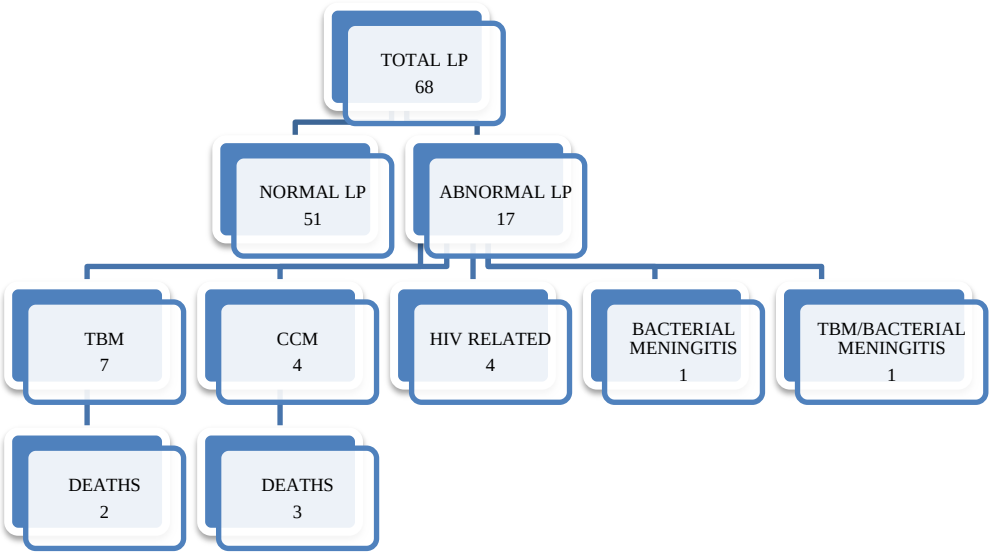
4.4 List of Figures:

4.4.1 Figure 1. Results of cranial CTs



SOL= Space Occupying Lesion
*Patients may have had multiple pathologies

4.4.2 Figure 2. Description of LP findings



4.5 Journal submission guidelines

Instructions to authors for Publication-ready format, taken from:

1. South African Journal of HIV Medicine, Submissions, Author Guidelines. Available from http://www.sajhivmed.org.za/index.php/hivmed/pages/view/authors (Accessed November 2014)

2. International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Manuscript Preparation and Submission: Preparing a Manuscript for Submission to a Biomedical Journal. Available from: http://www.icmje.org/manuscript_1prepare.html