DISSERTATION FOR THE MASTER OF MEDICINE (MMED) DEGREE

Dr Sharania Moodley

THE ASSOCIATION BETWEEN HEADACHE PRESENTATION, CLINICAL EXAMINATION AND NEUROIMAGING FINDINGS: A RETROSPECTIVE ANALYSIS OF PATIENTS PRESENTING TO A TERTIARY REFERRAL CENTRE

by

Dr Sharania Moodley

Submitted in partial fulfilment of the academic requirements
for the degree of MMed
in the Department of Neurology
School of Clinical Medicine
College of Health Sciences
University of KwaZulu-Natal
Durban
2021

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

Signed: [redacted] Name: A I BHIGJEE Date: 26/01/2022

Declaration

I, Dr Sharania Moodley, declare that

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

(iii) This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

(iv) This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

a) their words have been re-written but the general information attributed to them has been referenced;

b) where their exact words have been used, their writing has been placed inside quotation marks, and referenced.

(v) Where I have reproduced a publication of which I am an author, co-author or editor, I have indicated in detail which part of the publication was actually written by myself alone and have fully referenced such publications.

(vi) This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the dissertation and in the References sections.

Signed:  Date: 12/01/2022

Dedication

To my patients, thank you for allowing me to journey with you.

Acknowledgements

I acknowledge my supervisor, Professor Bhigjee, for the encouragement and precision in completing my dissertation.

Catherine Connolly for biostatistical input and to Dr K. Kistan for additional guidance.

The Biomedical Research Ethics Committee (BREC), University of Kwa-Zulu Natal for ethical approval to conduct the study.

The KZN Department of Health for approval to conduct the study.

The management of Inkosi Albert Luthuli Central Hospital for allowing me to use data and conduct this research at their institution.

Overview of thesis

Headaches are a global human experience. General practitioners, family physicians, emergency physicians, and neurologists are regularly faced with the dilemma of when or if neuroimaging is warranted in patients with headaches and a normal clinical examination. In resource constrained circumstances, additional guidance is necessary to determine if and when neuroimaging is indicated. In the absence of traditional red flags, the selection of patients for neuro-imaging is poorly defined. This study aims to identify the yield of neuroimaging findings in patients with headache and normal clinical examination and to identify additional red flags, if any, to guide clinical practice. There is a paucity of local data to guide practitioners in further managing and referring patients with headaches and a normal clinical examination. We also wanted to determine if international guidelines (American and European guidelines) are applicable to our local setting and essentially South Africa.

This study is a retrospective consecutive chart review of all patients assessed at a tertiary hospital (Inkosi Albert Luthuli Central Hospital, IALCH), in Kwa-Zulu Natal province in South Africa, presenting with a main complaint of headaches and a normal clinical examination from January 2008 to January 2018. Patients were included if they were 12 years and older with a main complaint of headaches, and had a normal neurological examination with neuroimaging performed at IALCH.

Data was collected for patient demographics, headache characteristics and neuroimaging outcomes. Neuroimaging findings were further evaluated in two categories: normal or unexpected and normal variants. The cost of normal neuroimaging was also evaluated to determine the cost to state sector.

A sample of 114 patients presenting with headache and findings of a normal clinical examination was required to estimate the proportion of participants with unexpected and normal variants findings on neuroimaging to within ± 13% (37% - 63%) with probability of 95% and assuming an uninformed percentage of 50%.

The total cohort of 114 patients had a mean age of 37.9 years and 42.3 years in the unexpected and normal variants imaging group. The cohort was made up of 70.2% (80 of 114) women and 82.5% (94 of 114) of patients presenting with headaches being younger than 50 years. Only 6 of 114 (5.3%) patients of cohort were known to be Human Immunodeficiency Virus (HIV) seropositive and 22 of 114 patients (19.3%) confirmed HIV seronegative.

This study revealed 23 of 114 (20.2%) patients with any unexpected findings together with normal variants (anatomical variants that do not have the potential to cause symptoms and do not need any therapeutic intervention). Most patients in the unexpected and normal variants group were between 41-50 years of age (47.8%, 11 of 23) and only 17.4% (4 of 23) were older than 50 years of age. Women made up 65.2% (15 of 23) and HIV seropositive patients made up 8.7% (2 of 23).

The most common unexpected findings were calcified granuloma (5.3%, 6 of 114) and sinus disease (3.5%, 4 of 114). The vascular unexpected findings were 2.6% (3 of 114%), neoplastic unexpected findings were 0.9% (1 of 114) and non-neoplastic unexpected findings were 15.8% (18 of 114). Normal variants include 0.9% (1 of 114). See Supplementary table 1.

On further statistical analysis, male patients were found to have a greater chance of having an unexpected or normal variant on neuroimaging. The difference in the presence and absence of nausea and vomiting in normal versus unexpected and normal variant group was found to be significant. More patients in the unexpected and normal variant group did not have nausea and vomiting. There is low sensitivity 20% and high negative predictive value of 77% for this symptom (see supplementary table 2). There was no association with age and unexpected findings or normal variant. The chances of unexpected findings or normal variant are almost twice as great in HIV seropositive compared to HIV seronegative patients but did not reach statistical significance.

We advise embracing a lower threshold to refer patients that are male, HIV seropositive patients, patients in the 41-50 year age group and patients with a change in headache frequency and intensity. Importantly, this study demonstrates that headache with nausea and vomiting in isolation, may be associated with normal neuroimaging reflecting primary type

headaches. In patients with headaches and a normal neurological examination, we advise referral of a subgroup of patients with primary headache disorders (trigeminal autonomic cephalalgias and migraine with aura).

This study reiterates the importance of a thorough physical examination and review of radiological guidelines to assist with investigating patients further. Unexpected neuroimaging findings like stroke and intracranial malignancies had low prevalence and systemic neuroimaging cannot be advocated in this setup and may in fact escalate cost both directly and indirectly

To our knowledge, this is the first study of this nature in South Africa and Africa, to determine the yield of neuroimaging findings of patients with headaches and normal clinical examination. These findings have far reaching implications for all practitioners, especially in resource limited settings.

Table of Contents

Part 1: Literature review

The purpose of this retrospective chart study is to evaluate the yield of normal neuroimaging findings in patients with headaches and normal clinical examination in adults reviewed at tertiary centre from 2008 to 2018.

1.1 International burden of headaches

Headaches may result in absenteeism, presenteeism, disability, increase in cost to hospitals by way of visits and investigations, and/or adverse effects from such investigations.
The Global burden of disease 2019 reported headache disorders ranked 14th among global causes of disability-adjusted life years (DALYs) for all ages and both genders. (1) Migraine has been found to be the leading cause of DALYs in young women and it is responsible for more years of lost healthy life in this group. (1) Global Campaign against Headache demonstrated that headache disorders were associated with impaired quality of life, substantial lost productivity, and high economic costs in every country assessed (table 1). (2) In England, migraine alone is responsible for an annual loss of 25 million days from work or school and is also associated with an annual cost of about 17 billion dollars in the United States of America. (3, 4)
A study by Callaghan *et al* highlighted that neuroimaging was frequently ordered during outpatient headache visits and this contributed to almost 1 billion dollars in annual costs. (5)

Table 1: Lost productive time from paid and household work as proportions of the total available time, and lost GDP, due to headache: country estimates from Lifting The Burden cross-sectional studies using standardised methodology (Table 2 from Saylor D, Steiner TJ. The Global Burden of Headache. Semin Neurol. 2018;38(2):182-90.), permission obtained.

Country	Per person lost productive time								Overall lost GDP
	From paid work				From household work				
	Migraine (%)	Tension-type headache (%)	All headaches on ≥15 d/m (%)	Probable MOH (%)[a]	Migraine (%)	Tension-type headache (%)	All headaches on ≥15 d/m (%)	Probable MOH (%)[a]	
European Region									
Lithuania	4	1	4	6	5	2	11	14	1.5
Russia	3	1	9	–	3	2	11	–	1.8
Western Pacific Region									
China	4	3	7	–	4	2	6	--	1.9
South East Asian Region									
India	2	1	8	6	2	1	5	11	1.7
Nepal	3	1	–	12	4	1	–	10	–
African Region									
Ethiopia	5	2	8	29	5	1	11	16	1.6
Zambia	6	2	–	7	5	1	–	5	1.9

Abbreviations: GDP, gross domestic product; MOH, medication-overuse headache.
[a]MOH in *Lifting The Burden* studies is reported as "probable MOH" (headache on ≥15 days per month associated with medication overuse) because, in cross-sectional studies, causation cannot be ascertained.

1.2 Prevalence and incidence of headaches

There is a lifelong prevalence of 96% (6) and estimated worldwide prevalence of 50% by the World Health Organisation (WHO)**.** (7) There were 1 billion prevalent cases, 87.6million incident cases, and 42.1million years lived with disability (YLD) for migraine in 2019. (1)

The 2018, Lifting the Burden organisation, together with WHO, completed population-based studies to determine the prevalence of headaches worldwide. The studies have demonstrated a high prevalence of headache disorders, including migraine, tension type headache (TTH), and medication-overuse headache (table two). Region specific results from the population based studies are outlined in table one and two. (2)

Concentrating on the African region, Ethiopia and Zambia revealed one-year headache prevalence of all headaches was only 45% in Ethiopia compared with 62% in Zambia. Migraine (18 vs. 23%) and TTH (21 vs. 23%) were similar in the two countries. Probable medication overuse headache is an urban problem. Zambia is much more urbanised than Ethiopia and this was reflected in probable medication overuse headaches found to be more prevalent in Zambia at 7.1% compared to 0.7% in Ethiopia.

Table 2: Global 1-year prevalence of headache disorders: country estimates from Lifting The Burden cross-sectional studies using standardised methodology (Table 1 from Saylor D, Steiner TJ. The Global Burden of Headache. Semin Neurol. 2018;38(2):182-90.), permission obtained.

Table 1 Global 1-year prevalences of headache disorders: country estimates from Lifting The Burden cross-sectional studies using standardized methodology

Country	All headaches (%)	Migraine (%)	Tension-type headache (%)	All headaches on ≥15 d/m (%)	Probable MOH (%)[a]
European Region					
European Union	79	35	38	7	3
Georgia	61	16	37	8	1
Lithuania	75	19	42	9	3
Moldova	53	18	18	5	–
Russia	62	20	31	10	7
Western Pacific Region					
China	24	9	11	1	0.6
South East Asia Region					
India	64	25	35	3	1
Nepal	85	35	41	8	2
Eastern Mediterranean Region					
Pakistan	77	22	45	7	1
Africa Region					
Ethiopia	45	18	21	3	1
Zambia	62	23	23	12	7

Abbreviation: MOH, medication-overuse headache.
[a]MOH in *Lifting The Burden* studies is reported as "probable MOH" (headache on ≥15 days per month associated with medication overuse) because, in cross-sectional studies, causation cannot be ascertained.

1.3 Classification of Headache disorders

Headache disorders have been recently classified, in the third edition of the International Classification of Headache Disorders, into primary, secondary, painful cranial neuropathies, other facial pain and other headache disorders.(8) This classification guides management, for instance, once the secondary type of headache disorders are classified, they are more likely to be neuroimaged. Primary headache disorders include migraine, tension-type headaches and trigeminal autonomic cephalalgias and other primary headache disorders.

1.4 The practitioners dilemma

Practitioners often refer patients for neuroimaging due to fear of missing a serious underlying treatable cause, subsequent medico-legal repercussions, disability caused by headaches and resultant medication overuse. The practitioner plays an important role in the initial clinical assessment as serious illness can be detected despite normal imaging. (9) Moreover, a normal investigation does not eliminate the need for further follow up and appropriate management of headache.

Magnetic resonance imaging (MRI) of the brain is frequently done for primary headaches and 90% of all primary type headaches will not reveal anything.(10) However, practitioners image patients with MRI scans to reassure the patient, practitioners quest for diagnostic certainty; poor cognitive reasoning; busy practice conditions where tests are ordered as a shortcut; financial incentives; professional peer pressure where recommendations for routine tests are expected as a demonstration of competence.(10) Defensive medicine may be reduced if clinicians are shielded by law when practicing evidence-based medicine in accordance with published guidelines.(11)

A modified table (12) from Frishberg BM describes the utility of benefits versus harms of patients neuroimaged with headaches and normal neurologic examination. The discovery of potentially treatable lesions when assessed with computed tomography (CT) scan in migraine was 0.3% and 0.4% with MRI. In patients with any headache, this increased to 2.4% for both CT brain (CTB) and MRI. Relief from anxiety was 30% for both MRI and CTB. The iodine reaction was mild in 10%, moderate in 1% and severe 0.01% and death 0.002%. Mild claustrophobia was found in 5% of patients that had a CT, and 5-15% for MRI, moderate

(requiring sedation) claustrophobia was 1% for CT and 5-10% for MRI and severe (unable to comply) 1-2% for CT.

1.5 Diagnosis of headaches

Referral of all patients with a main complaint of headache may not be possible; therefore it is essential to know which category of patients to refer for possible neuroimaging. Obtaining a detailed history of the patient's symptoms and clinical examination are the most important aspects in diagnosing headaches and further classifying headache type. (13)

Primary headache disorders, namely migraine and tension type headaches, are the most common type of headache disorder. (14) Holle *et al* advocated that patients with classic migraine or tension type headache do not require neuroimaging as part of their work up as these patients do not have a higher rate of relevant cerebral pathology when compared to the general population. (15).

The percentage of abnormal scans was found to be higher when ordered by neurologists (16). A recent study however revealed that that 6 of the 7 patients with a significantly abnormality on CT were assessed as having a normal neurological examination by a neurologist prior to scanning. (17)Therefore the sensitivity to detect neurological deficits was shown to be the same with emergency department doctors.

1.6 Neuroimaging guidelines

The research studies on the yield of abnormal neuroimaging investigations in patients presenting with headaches, and normal neurological examination depend on several factors (type of scan, duration of headache, study design, who orders the scan). (18)

Headache neuroimaging utilization was analysed by Callaghan *et al* and highlighted the routine practice of neuroimaging patients with primary headaches. (19)
Fouche *et al* in the Western Cape, South Africa reviewed the appropriateness of computed tomography (CT) and magnetic resonance imaging (MRI) scans. They found the most inappropriately requested scans were CT brain and provide local evidence across disciplines for inappropriate brain imaging. (20)

The United Kingdom National Clinical Guidelines centre advises the traditional method of diagnosing primary headaches does not require neuroimaging and imaging should therefore be avoided as it is unlikely to change management or reveal abnormalities. (21)

The American College of Radiology (ACR) Appropriateness Criteria—Headache Clinical Variants (revised in 2019) provides recent evidence-based guidelines on imaging in patients with headaches (22). They have identified common clinical scenarios and advise on the most appropriate imaging (if any), based on current literature.

In patients with new headache and normal neurologic examination, classic migraine or tension type primary headaches, the ACR in the Choosing wisely campaign, advise neuroimaging for primary headaches is not necessary. (22) In patients with new primary migraine or tension-type headache with normal neurologic examination, or chronic headache with no new feature, initial imaging is usually not appropriate.
Patients with a new primary headache suspected of trigeminal autonomic origin, MRI brain is usually appropriate as initial imaging. (22) MRI brain is usually appropriate for the initial imaging in patients with a new primary headache of suspected trigeminal autonomic origin, as there is an unexplained association with pituitary macroadenomas in 4% of patients. (23)
Initial imaging is usually not appropriate in patients with chronic headache, no new features and no neurologic deficit. However if there is an increase in frequency in chronic headaches and new features, MRI brain is usually appropriate as initial imaging. (22)

Guidelines for neuroimaging in headaches (2019) by the British Society of Neuroradiologists Standards Subcommittee advise neuroimaging may be considered if a patient is disabled by fear of serious pathology. (24)

European Headache Foundation Consensus Guidelines in 2016 provided expert opinion guidelines. (25) If the patient has symptoms or signs creating doubt of the primary origin of the headache, then these patients should be neuroimaged. These consensus guidelines advise that in adult patients with migraine and no recent change in attack pattern, no seizures, and absence of focal neurological symptoms or signs, the routine use of neuroimaging is not warranted. (25) In the case of migraine with aura, persistent on one side or brainstem aura, patients should be neuroimaged with brain MRI.
Persistent aura without infarction and migrainous infarction require brain MRI scanning (including MR venogram (MRV) and MR angiogram (MRA)). Patients with trigeminal autonomic cephalalgias, brain imaging with MRI with focus on the pituitary and cavernous sinus is recommended. (25)

1.7 Other rare causes of headaches with a normal examination

Systemic malignancy with resultant neoplastic meningitis (26) and chronic daily headaches in menopausal or perimenopausal patients are rare causes for headaches with a normal neurological examination. (27)

The common concerns when encountering a patient with headaches is subarachnoid haemorrhage, aneurysms and tumour. The incidence of subarachnoid haemorrhage (SAH) in patients with sudden severe headache and a normal neurological examination may be as high as 10%.(28) Patients with acute onset headaches, elevated blood pressures, neck stiffness and altered mental state may also prompt further referral. Cerebral venous thrombosis (CVT) is another life threatening entity that clinicians do not want to miss. A CVT may present with an isolated headache which is thunderclap in nature and should be further investigated with a CT brain. However, CT brain may be normal and an MRI or MR venogram should be performed if clinical suspicion persists. (29).

The presence of a brain tumour is one of the greatest concerns for patients with headaches. The risk of a brain tumour increases with age and the presentation with an isolated headache can range between 2% and 16%.(30) A study by Carey *et al* revealed the diagnosis of malignancy was rare in individuals presenting with incident headache and early neuroimaging (within 30 days of headache) lead to a small reduction in time to diagnosis. Interestingly, risk of death was higher in the early neuroimaging group compared to the referent group, and the authors postulate higher disease severity in this group.(31) Alons *et al* described the utility of CT angiogram in patients with acute severe headache, normal neurological examination and further normal non-contrasted CT brain in a meta-analysis. This group demonstrated that the number needed to scan to find a clinically relevant abnormality and likely cause of the headache on CT angiogram was 61 and the number needed to scan for any abnormality was 14. Therefore the diagnostic yield of CT angiogram is limited, however given the consequences for further treatment (subarachnoid haemorrhage, cerebral venous thrombosis (CVT), cervical arterial dissection); it may be justified in the emergency setting. (32)

1.8 Outcomes from previous studies

Neuroimaging findings in headache with normal neurologic examination: systematic review and meta-analysis by Kamtchum-Tatuene *et al* (33), reviewed 41 studies (15760 patients) up to September 2017 and found an overall prevalence of unexpected findings and normal variants was 17.5%(95% CI: 13.1-22.3). Sinusitis (8.6%) and white matter abnormalities (7.4%) were the single most prevalent unexpected findings and prevalence of vascular unexpected findings (5.7%) was found to increase with the proportion of migraine patients in the study population and with age.
The findings included vascular, neoplastic, and non-neoplastic changes and prevalence of these findings were 6.6%, 1.4%, and 9.6% respectively. This group also found that patients with a higher proportion of migraine with aura, was associated with a higher prevalence of vascular unexpected findings. This may suggest that this subgroup of patients may require more specific neuroimaging criteria. This study concluded that these important findings are rare in patients with headache and normal neurologic examination and are better detected on MRI. The findings supported the recent American and European radiological guidelines. Important aspects of this article describe the definitions for unexpected findings, normal variants, and unexpected findings.

Normal variants: anatomical variants that do not have the potential to cause symptoms and do not need any therapeutic intervention.

Unexpected findings, in the context of a normal neurologic examination, were defined as any neuroimaging finding distinct from known and well-characterized normal variants, irrespective of the potential relationship with the headache or the subsequent management. The unexpected findings are further classified as vascular, neoplastic and non-neoplastic.

This meta-analysis published in 2020, describes a prevalence of all-type stroke that is nearly 4 times higher in studies with a mean age ≥ 40 years when compared to studies with a mean age < 40 years (3.0% versus 0.8%. As a result, the age of ≥ 40 years should be considered as a red flag in patients with headache, although the difference was not found to be significant.

MRI based studies revealed a higher prevalence of unexpected findings, with better detection of the white matter abnormalities and non-neoplastic lesions, while the prevalence of neoplastic unexpected findings remained fairly unchanged.

There was a significant association between a higher proportion of migraine patients and higher prevalence of vascular unexpected findings. The specific prevalence of the vascular unexpected findings remains too low to justify systemic imaging especially in migraine patients, with a normal examination and no further red flags.

This study also found migraine was not specifically associated with cerebral blood vessel abnormalities, neoplasms, or other non-neoplastic unexpected findings which supports the current neuroimaging guidelines.
Despite the above statement, this study emphasizes that patients with migraine and associated aura seem to be a high risk subgroup. Physicians should therefore have a low threshold of to neuroimage patients with migraine with aura. Neuroimaging should preferably be an MRI brain according to the American Headache Society Choosing Wisely Recommendations (34) and the European Headache Foundation Consensus Guidelines (25).

The study further emphasizes that practitioners should search for specific red flags which include: atypical aura with neurologic deficit following rather than preceding headache onset or lasting more than 60 minutes, new onset of aura in a patient previously known for migraine without aura, exacerbation of the migraine (pain frequency or intensity) independent of the usual triggers, combination with cardiovascular risk factors, family history of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), personal history of stroke, transient ischemic attack, or reversible cerebral vasoconstriction syndrome (33).

Jang *et al* reviewed neuroimaging in headache patients and the outcomes including clinically significant neurological abnormalities. They included ten studies, 2377 patients and determined a pooled prevalence of detecting clinically significant abnormalities in headache patients that were neuroimaged to be 8.86% (95% confidence interval: 5.12–15.33%) in primary headache patients. (21) This systemic review included primary headaches, acute severe headache onset and chronic headache onset. In this study, a slightly higher prevalence of detecting a significant neurological abnormality was found in the acute onset headache patients compared to the non-acute group. The results also suggest a greater probability of an intracranial abnormality in older patients, specifically patients that are 40 years and older.

The prevalence of intracranial diseases were categorized into four groups: highest prevalence of cerebrovascular disease was highest [4.31% (95% CI: 2.01–9.24%)], followed by brain space-occupying lesions [1.35% (95% CI: 0.59– 3.11%)], infectious/inflammatory disease [0.72% (95% CI: 0.20–2.57%)], and congenital human brain malformations [0.36% (95% CI: 0.16–0.81%)].

This study recommends careful and limited use of neuroimaging in patients with headaches. In patients with acute onset of headaches who present to an emergency department, angiography testing may be useful in detected vascular abnormalities however this requires further research.

Goldstein *et al* (17) retrospectively reviewed CT head findings in 2015 in the emergency department for patients with atraumatic headache and a normal neurological examination. There are concerns of increasing neuroimaging investigations as initial imaging, and the cases of significant intracranial pathology are decreasing. The concerns are that there is overuse of neuroimaging and increased exposure to medical ionised radiation with risk of radiation induced cancer. They included 422 patients and 43.4% of scans were normal. There were 257 (60.9%) patients that were female in the cohort and median age was 44.9 years, average age was 48.2 (range 18.5– 96.1) years. Most abnormalities found were sinusitis (35%) or ischaemic changes. Seven scans showed significant changes (1.6%) requiring immediate change in management. Clinically significant CT abnormalities were more prevalent in males; however this was not statistically significant. All patients described their pain as severe and non-remitting, 3 patients had vomiting and 3 were woken up by headache. This study concludes that a normal neurological examination does not rule out secondary causes and the potential for harm from radiation delivered should be weighed against the potential benefit. The risk of developing cancer form a single CT head scan is low. (35) CT scan in the emergency department should also be performed for patients with severe and non-remitting headaches with no prior neuroimaging available.

Rai *et al,* carried out a retrospective observational study reviewing 500patients with headaches, who underwent CT or MRI scan of head over a 2 year period. Patients were divided into two groups, one with red flags present and one group with no red flags. There were 48 patients with red flags and 29 of these 48 patients (60.4%) found to have a positive scan (that is, not a normal scan). The group with no red flags was made up 452 patients and

97out of 452 patients (21.5%) had positive scans. This difference in the two groups was found to be statistically significant. The pathology seen in the 500 cases included 29 (5.8%) patients had some type of brain parenchymal pathology and extra cerebral pathology were seen in 97 cases (sinusitis in 58 (11.6%), bone related pathology in 26 (5.2%) and chronic suppurative otitis media (CSOM) in 13 (2.6%) patients). This study concluded that neuroimaging in the absence of red flags yields a very low percentage of clinically significant positive findings.

A study by Evans looked at the incidental findings and normal anatomical variants on adult MRI brain. There were 21 types of such findings with each reviewed in detailed: aneurysms, arachnoid cysts, Cavum Septum Pellucidi (CSP) and Cavum Vergae (CV), Cerebral Vascular Malformations, Chiari Malformations, Empty Sella Turcica, Gray Matter Heterotopia, Mastoiditis, Mega Cisterna Magna, Meningioma, Normal Variants of the Cerebral Circulation, Paranasal Sinuses abnormalities, Pineal Cysts, Pituitary Tumors, Radiologically Isolated Syndrome, Rathke's Cleft Cysts, Sagittal Sinus Venous Lake, Vein of Galen Aneurysm, Vestibular Schwannomas, Virchow-Robin Space (VRS), White Matter Abnormalities (WMA). (36)

A prospective study published by Sempere *et al*, determined the frequency of significant intracranial lesions in patients with non-acute headache and normal neurologic examination in search of neuroimaging guidance. (37) They detected significant lesions in 22 patients (1.2%, 95% confidence interval (CI) 0.7, 1.8). Abnormalities where divided into significant, non-significant or normal. The rate of the significant intracranial abnormalities in this study was 0.9% (95% CI 0.5, 1.4). The only variable that was associated with increased probability of intracranial abnormality was neurological examination. The study concluded that despite the proportion of patients with headache and intracranial lesions were relatively small, history and neurological examination cannot rule out these abnormalities.

1.9 Cost of Imaging

The cost of imaging may be evaluated as tangible and less tangible (reduced quality of life) measures. The selective use of neuroimaging in primary headaches is important as it is not cost effective and it can cause patient anxiety, radiation exposure or contrast related adverse effects, implications on future insurance applications and possibility of false-positive results. (21) Incidental findings can result in further unnecessary investigations, and these findings may not account for presenting symptoms. (15) This will result in both direct and indirect increase in costs. Whilst the cost of imaging is often emphasized, the value of a negative scan should not be underestimated providing both patient and clinician reassurance.

1.10 Red flags

The European headache federation consensus on the investigation of primary headache disorders include the following red flags: new onset headache, change in previously stable headache pattern, headache that abruptly reaches the peak level, headache that changes with posture, headache awakening the patient, or precipitated by physical activity or Valsalva manoeuvre, first onset of headache ≥50 years of age, neurological symptoms or signs, trauma, fever, seizures, history of malignancy, history of HIV or active infections, and prior history of stroke or intracranial bleeding.(25)

In 2003, a mnemonic 'SNOOP' (systemic illness, neurologic signs, onset pattern, older age, pattern change) was developed as red flag indicators in guiding further referral and neuroimaging (38) This has been modified to the SNNOOP10 (39) which include systemic symptoms including fever; neoplasm history; neurologic deficit (including decreased consciousness); sudden or abrupt onset; older age (onset after 65 years); pattern change or recent onset of new headache; positional headache; precipitated by sneezing, coughing, or exercise; papilloedema; progressive headache and atypical presentations; pregnancy or puerperium; painful eye with autonomic features; posttraumatic onset of headache; pathology of the immune system such as HIV; painkiller overuse or new drug at onset of headache. Regarding primary headaches, trigeminal autonomic cephalalgias and patients experiencing migraine with a change in aura should be referred for assessment and neuroimaging. These

positive visual symptoms may reflect an occipital lobe lesion and will therefore require neuroimaging with an MRI. (40)

1.11 Knowledge gap

In South Africa and in Africa there are no studies to show the yield of neuroimaging studies and whether these are comparative with the rest of the world. Further, the guidelines that are available are internationally based, and some are developed on consensus basis. Are the available guidelines applicable to our local setting? In resource constrained facilities, Healthcare professionals require further guidelines to advise on neuroimaging in headache patients.

1.12 References

1. Safiri S, Pourfathi H, Eagan A, Mansournia MA, Khodayari MT, Sullman MJM, *et al*. Global, regional, and national burden of migraine in 204 countries and territories, 1990 to 2019. PAIN. 9000. https://doi.org/10.1097/j.pain.0000000000002275
2. Saylor D, Steiner TJ. The Global Burden of Headache. Semin Neurol. 2018;38(2):182-90. https://doi.org/10.1055/s-0038-1646946
3. Goldberg LD. The cost of migraine and its treatment. Am J Manag Care. 2005;11(2 Suppl):S62-7. https://doi.org/10.37765/ajmc.2020.42543
4. Steiner TJ, Scher AI, Stewart WF, Kolodner K, Liberman J, Lipton RB. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia. 2003;23(7):519-27. https://doi.org/10.1046/j.1468-2982.2003.00568.x
5. Callaghan BC, Kerber KA, Pace RJ, Skolarus LE, Burke JF. Headaches and neuroimaging: high utilization and costs despite guidelines. JAMA internal medicine. 2014;174(5):819-21. https://doi.org/10.1001/jamainternmed.2014.173
6. Rizzoli P, Mullally WJ. Headache. Am J Med. 2018;131(1):17-24. https://doi.org/10.1212/01.wnl.0000072526.35698.0a
7. WHO. Headache disorders: World Health Organization; 2016(updated April 2016; cited 2017 6th October). 2016 http://www. who.int/ mediacentre/ factsheets/ fs277/ en/. https://www.who.int/news-room/fact-sheets/detail/headache-disorders
8. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. https://doi.org/10.1177/0333102417738202
9. Neuroimaging for the evaluation of chronic headaches: an evidence-based analysis. Ont Health Technol Assess Ser. 2010;10(26):1-57. Epub 2010 Dec 1. PMID: 23074404; PMCID: PMC3377587 http://www.ncbi.nlm.nih.gov/pmc/articles/pmc3377587/
10. Evans RW. Diagnostic testing for migraine and other primary headaches. Neurol Clin. 2009;27(2):393-415. https://doi.org/10.1016/j.ncl.2008.11.009
11. Jordan JE, Flanders AE. Headache and Neuroimaging: Why We Continue to Do It. AJNR Am J Neuroradiol. 2020;41(7):1149-55. https://doi.org/10.3174/ajnr.a6591
12. Evans RW. Diagnostic testing for headache. Med Clin North Am. 2001;85(4):865-85. https://doi.org/10.1016/s0025-7125(05)70348-5

13. Sandrini G, Friberg L, Jänig W, Jensen R, Russell D, Sanchez del Rìo M, *et al*. Neurophysiological tests and neuroimaging procedures in non-acute headache: guidelines and recommendations. Eur J Neurol. 2004;11(4):217-24. https://doi.org/10.1111/j.1468-1331.2003.00785.x

14. Kenteu B, Fogang YF, Nyaga UF, Zafack JG, Noubiap JJ, Kamtchum-Tatuene J. Neuroimaging of headaches in patients with normal neurological examination: protocol for a systematic review. BMJ Open. 2018;8(2):e020190. https://doi.org/10.1136/bmjopen-2017-020190

15. Holle D, Obermann M. The role of neuroimaging in the diagnosis of headache disorders. Ther Adv Neurol Disord. 2013;6(6):369-74. https://doi.org/10.1177/1756285613489765

16. Baker HL, Jr. Cranial CT in the investigation of headache: cost-effectiveness for brain tumors. J Neuroradiol. 1983;10(2):112-6. https://pubmed.ncbi.nlm.nih.gov/6410008/

17. Goldstein L, Laytman T, Steiner I. Is Head Computerized Tomography Indicated for the Workup of Headache in Patients with Intact Neurological Examination. Eur Neurol. 2018;80(5-6):341-4. https://doi.org/10.1159/000496805

18. Frishberg BM. The utility of neuroimaging in the evaluation of headache in patients with normal neurologic examinations. Neurology. 1994;44(7):1191-7. https://doi.org/10.1212/wnl.44.7.1191

19. Callaghan BC, Kerber KA, Pace RJ, Skolarus L, Cooper W, Burke JF. Headache neuroimaging: Routine testing when guidelines recommend against them. Cephalalgia. 2015;35(13):1144-52. https://doi.org/10.1001/jamainternmed.2014.173

20. Fouche PE, Jenkins LS, Vermeulen A. Appropriateness of computed tomography and magnetic resonance imaging scans in a rural regional hospital in South Africa: A 6-year follow-up study. S Afr Med J. 2020;111(1):46-51. https://doi.org/10.7196/samj.2020.v111i1.14860

21. Jang YE, Cho EY, Choi HY, Kim SM, Park HY. Diagnostic Neuroimaging in Headache Patients: A Systematic Review and Meta-Analysis. Psychiatry investigation. 2019;16(6):407-17. https://doi.org/10.30773/pi.2019.04.11

22. Whitehead MT, Cardenas AM, Corey AS, Policeni B, Burns J, Chakraborty S, *et al*. ACR Appropriateness Criteria® Headache. J Am Coll Radiol. 2019;16(11s):S364-s77. https://doi.org/10.1016/j.jacr.2019.05.030

23. Levy MJ, Matharu MS, Meeran K, Powell M, Goadsby PJ. The clinical characteristics of headache in patients with pituitary tumours. Brain. 2005;128(Pt 8):1921-30. https://doi.org/10.1093/brain/awh525

24. US Headache Consortium. Evidence-based guidelines in the primary care setting: neuroimaging in patients with nonacute headache. [cited 16 Oct 2008]. Available from url: http://www.americanheadachesociety.org/professionalresources/USHeadacheConsortiumGuide lines.asp

25. Mitsikostas DD, Ashina M, Craven A, Diener HC, Goadsby PJ, Ferrari MD, *et al*. European Headache Federation consensus on technical investigation for primary headache disorders. J Headache Pain. 2015;17:5. https://doi.org/10.1186/s10194-016-0596-y

26. Elliott P, Ku NN, Werner MH. Neoplastic meningitis with normal neurological findings. Magnetic resonance imaging results. J Neuroimaging. 1995;5(4):233-6. https://doi.org/10.1111/jon199554233

27. Rozen TD. A New Subtype of Chronic Daily Headache Presenting in Older Women. J Womens Health (Larchmt). 2018;27(2):203-8. https://doi.org/10.1089/jwh.2017.6460

28. Cooper JG, Smith B, Hassan TB. A retrospective review of sudden onset severe headache and subarachnoid haemorrhage on the clinical decision unit: looking for a needle in a haystack? Eur J Emerg Med. 2016;23(5):356-62. https://doi.org/10.1097/mej.0000000000000266

29. Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. Journal of Neurology, Neurosurgery & Psychiatry. 2005;76(8):1084-7. http://dx.doi.org/10.1136/jnnp.2004.056275

30. Kernick DP, Ahmed F, Bahra A, Dowson A, Elrington G, Fontebasso M, *et al*. Imaging patients with suspected brain tumour: guidance for primary care. Br J Gen Pract. 2008;58(557):880-5. https://doi.org/10.3399/bjgp08x376203

31. Carey MR, Callaghan BC, Kerber KA, Skolarus LE, Burke JF. Impact of early headache neuroimaging on time to malignant brain tumor diagnosis: A retrospective cohort study. PLoS One. 2019;14(2):e0211599. https://doi.org/10.1371/journal.pone.0211599

32. Alons IME, Goudsmit BFJ, Jellema K, van Walderveen MAA, Wermer MJH, Algra A. Yield of Computed Tomography (CT) Angiography in Patients with Acute Headache, Normal Neurological Examination, and Normal Non Contrast CT: A Meta-Analysis. J Stroke Cerebrovasc Dis. 2018;27(4):1077-84. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.11.016

33. Kamtchum-Tatuene J, Kenteu B, Fogang YF, Zafack JG, Nyaga UF, Noubiap JJ. Neuroimaging findings in headache with normal neurologic examination: Systematic review and meta-analysis. J Neurol Sci. 2020;416:116997. https://doi.org/10.1016/j.jns.2020.116997

34. Loder E, Weizenbaum E, Frishberg B, Silberstein S. Choosing wisely in headache medicine: the American Headache Society's list of five things physicians and patients should question. Headache. 2013;53(10):1651-9. https://doi.org/10.1111/head.12233

35. Smith-Bindman R, Lipson J, Marcus R, Kim KP, Mahesh M, Gould R, *et al*. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med. 2009;169(22):2078-86. https://doi.org/10.1001/archinternmed.2009.427

36. Evans RW. Incidental Findings and Normal Anatomical Variants on MRI of the Brain in Adults for Primary Headaches. Headache. 2017;57(5):780-91. https://doi.org/10.1111/head.13057

37. Sempere AP, Porta-Etessam J, Medrano V, Garcia-Morales I, Concepción L, Ramos A, *et al*. Neuroimaging in the evaluation of patients with non-acute headache. Cephalalgia. 2005;25(1):30-5. https://doi.org/10.1111/j.1468-2982.2004.00798.x

38. Dodick D, editor Diagnosing Headache : Clinical Clues and Clinical Rules2003. https://www.semanticscholar.org/paper/Diagnosing-Headache-%3A-Clinical-Clues-and-Clinical-Dodick/8f11dd601f346b88c83cd353e1331d812a82ee39

39. Do TP, Remmers A, Schytz HW, Schankin C, Nelson SE, Obermann M, *et al*. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. Neurology. 2019;92(3):134-44. https://doi.org/10.1212/wnl.0000000000006697

40. Micieli A, Kingston W. An Approach to Identifying Headache Patients That Require Neuroimaging. Frontiers in public health. 2019;7:52. https://doi.org/10.3389/fpubh.2019.00052

Part 2: A submission ready manuscript

Title: The association between headache presentation, clinical examination and neuroimaging findings: A retrospective analysis of patients presenting to a tertiary referral centre

S Moodley[1], A.I Bhigjee[2]

Authors:

1. Sharania Moodley - Neurology registrar; [MBChB (UKZN); DipPEC(SA)]
2. Ahmed I. Bhigjee - Emeritus Professor; [MBChB (Natal); MRCP (U.K.), PhD (Natal); FC Neurology(SA)]

Affiliations for all authors: Department of Neurology, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa

Corresponding author: Sharania Moodley
Email: sharmoodley@gmail.com
Address: Department of Neurology, Inkosi Albert Luthuli Central Hospital, Level 3.
800 Vusi Mzimela Road,
Cato Manor,
Durban, South Africa,
4091
Telephone: +2731 240 2359
Fax: +2731 240 2358

Word count (abstract): 245
Word count (Manuscript text excluding tables, figures and references): 3860
Number of figures: 1
Number of tables: 3

Competing interests: The author(s) declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article

Author contributions: S.M conceived the presented idea and developed the theory and performed the computations. A.I.B supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

Funding information: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author, S.M. The data are not publicly available as it may compromise the privacy of research participants.

Disclaimer: The views expressed in the submitted article are that of the authors and not an official position of the institution or funder.

Abstract

Background: Careful selection of patients with headaches and a normal clinical examination for neuroimaging is necessary as the worldwide burden of headaches is high.

Objectives: Determine the yield of neuroimaging findings in patients with headache and normal clinical examination.

Methods: A retrospective consecutive chart review of all patients with a main complaint of headaches and a normal clinical examination were assessed at a tertiary hospital, in Kwa-Zulu Natal province, South Africa, between January 2008 to January 2018.

Results: One hundred and fourteen patients were included into the study. The mean age of the total cohort was 37.9 years. The study consisted mainly of women (70.2%) and 17.4% of patients older than 50 years of age. Twenty-three of 114 patients (20.2%) were found to have unexpected or normal variant findings and 11 of 23patients (47.8%) were between 41-50 years of age. Women made up 65.2% (15 of 23patients) and HIV seropositive patients made up 8.7% (2 of 23 patients).

Thirteen of 114 patients (11.4%) required change in management. Two headache characteristics were statistically significant: nausea and vomiting (p= 0.009) and sharp type headaches (p=0.03) in unexpected and normal variant group. There was a higher chance of an abnormal neuroimaging study in men and HIV seropositive patients.

Conclusions: Findings suggest embracing a lower threshold to image patients that are male, HIV seropositive patients, patients in the 41-50 year age group. Importantly, this study demonstrates that headache with nausea and vomiting in isolation, may be associated with normal neuroimaging reflecting primary type headaches.

Keywords: Headache, normal clinical examination, neuroimaging, headache red flags

Introduction

Headaches are a global human experience. There is a lifelong prevalence of 96% (1) and estimated worldwide prevalence of 50% by the World Health Organisation (WHO).(2) Family physicians, emergency physicians, and neurologists are regularly faced with the dilemma of when or if neuroimaging is warranted in patients with headaches and a normal clinical examination. The decision to further refer and neuroimage is crucial as headaches can be benign or a prelude to a life threatening illness if not acted on timeously.

The Global burden of disease 2019 reported headache disorders ranked 14th among global causes of disability-adjusted life years (DALYs) for all ages and both genders.(3) In England, migraine alone is responsible for an annual loss of 25 million days from work or school and is also associated with an annual cost of about 17 billion dollars in the United States of America.(4,5)

The 2018, Lifting the Burden organisation, together with WHO, completed adult population-based studies and found high prevalence of headache disorders. There is a one year prevalence of all headaches 45% in Ethiopia compared with 62% in Zambia. Migraine (18 vs. 23%) and tension type headaches (21 vs. 23%) were similar in both countries.(6)

Practitioners often refer patients for neuroimaging due to fear of missing a serious underlying treatable cause, subsequent medico-legal repercussions, disability caused by headaches and resultant medication overuse. The selective use of neuroimaging in primary headaches is important as it is not cost effective and it can cause patient anxiety, radiation exposure or contrast related adverse effects, implications on future insurance applications and possibility of false-positive results.(7) Incidental findings can result in further unnecessary investigations, and these findings may not account for presenting symptoms.(8) This will result in both direct and indirect increase in costs.

A modified table (9) from Frishberg BM describes the utility of benefits versus harms of patient's neuroimaged with headaches and normal neurologic examination. The discovery of potentially treatable lesions when assessed with computed tomography (CT) in migraine was 0.3% and 0.4% with magnetic resonance imaging (MRI). This increased to 2.4% for both CT brain (CTB) and MRI for any headache. Relief from anxiety was 30% for both MRI and

CTB. The iodine reaction was mild in 10%, moderate in 1% and severe 0.01% and death 0.002%. Mild claustrophobia was found in 5% of patients that had a CT, and 5-15% for MRI, moderate (requiring sedation) was 1% for CT and 5-10% for MRI and severe (unable to comply) 1-2% for CT.

A study by Callaghan *et al* highlighted that neuroimaging was frequently ordered during outpatient headache visits and this contributed to almost 1 billion dollars in annual costs.(10) Whilst the cost of imaging is often emphasized, the value of a negative scan should not be underestimated providing both patient and clinician reassurance.

Referral of all patients with a main complaint of headache may not be possible; therefore it is essential to know which category of patients to refer. Obtaining a detailed history of the patient's symptoms and clinical examination are the most important aspects in diagnosing headaches and further classifying headache type.(11)

Headache disorders have been recently classified, in the third edition of the International Classification of Headache Disorders, into primary, secondary, painful cranial neuropathies, other facial pain and other headache disorders .(12) This classification aids in further management, for instance, the secondary type of headache disorders are more likely to be neuroimaged. Primary headache disorders, namely migraine and tension type headaches, are the most common type of headache disorder.(13) Holle *et al* advocated that patients with classic migraine or tension type headache do not require neuroimaging as part of their work up as these patients do not have a higher rate of relevant cerebral pathology when compared to the general population.(8) The United Kingdom National Clinical Guidelines centre advises the traditional method of diagnosing primary headaches does not require neuroimaging and imaging therefore should be avoided as it is unlikely to change management or reveal abnormalities.(7) These findings have not been validated in our local setting.

Headache neuroimaging utilization was analysed by Callaghan *et al* and highlighted the routine practice of neuroimaging patients with primary headaches.(14)
Fouche *et al* in the Western Cape, South Africa reviewed the appropriateness of CT and MRI scans. They found the most inappropriately requested scans were CT brains and provides local evidence across disciplines for inappropriate brain imaging.(15)

Other rare causes of headaches with a normal examination include systemic malignancy with resultant neoplastic meningitis (16) and chronic daily headaches in menopausal or perimenopausal patients.(17) Some traditional indicators of headache red flags in guiding further referral include the mnemonic 'SNOOP' (systemic illness, neurologic signs, onset pattern, older age, pattern change).(18) This has been modified to the SNNOOP10 list (19) which additionally include neoplasm history; recent onset of new headache; positional headache; precipitated by sneezing, coughing, or exercise; papilloedema; progressive headache and atypical presentations; pregnancy or puerperium; painful eye with autonomic features; posttraumatic onset of headache; pathology of the immune system such as HIV; painkiller overuse or new drug at onset of headache.

In South Africa and in Africa there are no studies to show the yield of neuroimaging studies and whether these are comparative with the rest of the world. Further the guidelines that are available are internationally based, and some are developed on a consensus basis. Are the available guidelines applicable to our local setting? In resource constrained facilities, Healthcare professionals require further guidelines to advise on neuroimaging in headache patients.

There is a paucity of local data to guide practitioners in further managing and referring patients with headaches and a normal clinical examination. Our study aimed to determine the correlation of neuroimaging findings in patients presenting with headaches and a normal clinical examination. Should there be a fair correlation, then patients with a normal examination can be managed safely with the general practitioner without imminent need for referral for neuroimaging.

The primary objectives were to determine the yield of neuroimaging findings in patients with normal clinical examination; and if the neuroimaging findings are clinically relevant. Secondary objectives aimed to identify additional red flags, if any, in patients with unexpected findings or normal variants and to estimate the cost to the state sector following further analysis of the scans.

Research method and design:

This study is a retrospective chart review of all patients assessed at a tertiary hospital with a main complaint of headaches and a normal clinical examination from January 2008 to

January 2018. The study setting was the Department of Neurology at Inkosi Albert Luthuli Central Hospital (IALCH), a tertiary referral centre for regional and district hospitals in Kwa-Zulu Natal province in South Africa.

Patients with ICD coding for headaches were retrieved for the study period. (Figure 2) Patients were included if they were 12 years and older with a main complaint of headaches, and had a normal neurological examination with neuroimaging performed at IALCH. Exclusion criteria included a history of cranial vault pathology and previous or current meningitis, headaches as a result of falls or trauma related injuries, post procedural headaches and pregnancy related headaches. If there were duplicate files, the file with the most information was reviewed. Patients were excluded if they had not been assessed by a doctor from the neurology department.

The initial documented assessment at the neurology clinic was analysed. Neuroimaging (CT and MRI) studies were performed at the hospital and these reports were reviewed. Data was collected for patient demographics (table 1) and headache characteristics (table 2). Neuroimaging findings were further evaluated as normal or unexpected findings or normal variants (table 3). During the study, terms such as 'abnormal' and 'incidental' were avoided and the' unexpected findings and normal variants' were used and better described the neuroimaging findings. This is because findings that were normal variants could not be deemed abnormal per se and all the other findings were classified as unexpected. This is in accordance with Kamtchum-Tatuene *et al* (20). However in daily practice, normal variants could be investigated with its unknown significance or relation to headache. Human Immunodeficiency Virus (HIV) status was determined by disclosure by patient or testing at the hospital. If neither was done, the HIV status remained unknown.

Data collection was captured on Microsoft Excel 2010. Percentages were rounded off to the nearest decimal. To maintain anonymity, patients were identified by a unique headache number. An application for full ethical approval was made to the Biomedical Research Ethics Committee (BREC) and ethics consent was received on 18 July 2019. The ethics approval number is 134/19.

Statistics:

A sample of 114 participants presenting with headache and findings of a normal clinical examination is required to estimate the proportion of participants with unexpected findings and normal variants neuroimaging findings to within ± 13% (37% - 63%) with probability of 95% and assuming an uninformed percentage of 50%. Sample size was estimated using Stata V13.1.

Statistical analysis

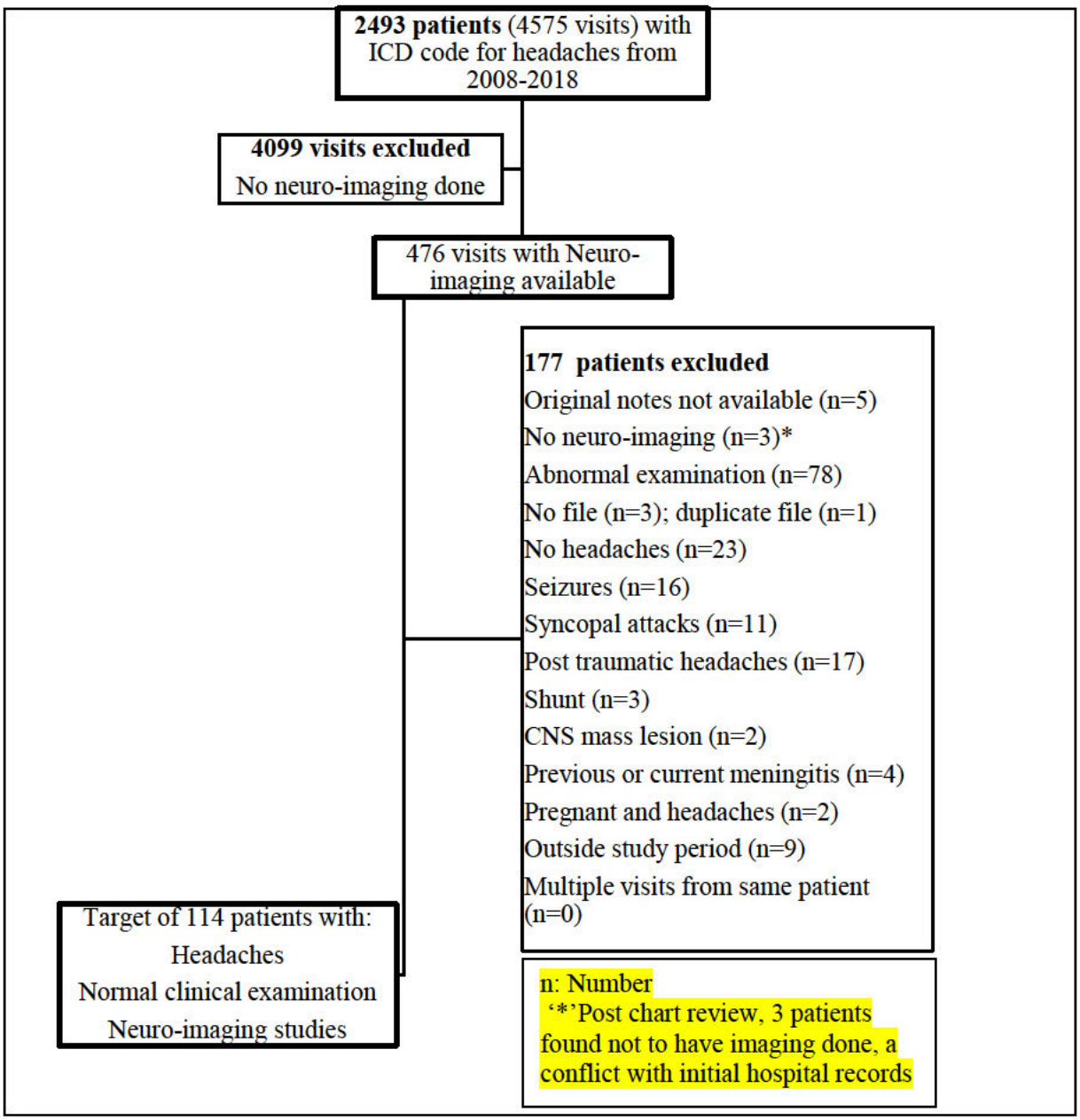
Descriptive statistics on the demographic and clinical characteristics of participants were reported. Factors associated with unexpected findings and normal variants were identified using Chi Square tests for categorical variables and t test or Wilcoxon rank sum tests/Kruskal-Wallis for ordinal and numeric variables depending on their distribution. The effect of gender, age and HIV status were examined in a logistic model. Only unadjusted odds ratios and 95% confidence limits were reported since no variable reached the inclusion criteria of $p < 0.3$. Data was analyzed using Stata Statistical software V15.1.

Results:

One hundred and fourteen consecutive patients with the main complaint of headache, normal neurological examination and neuroimaging was available for analysis and were retrospectively assessed at a tertiary centre over a 10 year period from January 2008 to January 2018 (figure 1).

Patients had a mean age of 37.9 years in the total cohort and 42.3 years in unexpected findings and normal variants neuroimaging group. The cohort was made up of mainly women (70.2%) with 82.5% of patients presenting with headaches being younger than 50 years (94/114). Only 6 of 114 (5.3%) patients of cohort were known HIV seropositive and 22 of 114 patients (19.3%) confirmed HIV seronegative.

Figure 1: Flow chart of data collection



Primary outcomes:

Twenty-three of 114 patients (20.2%) were found to have unexpected or normal variant findings and 11 of 23patients (47.8%) were between 41-50 years of age. Women made up 65.2% (15 of 23patients) and HIV seropositive patients made up 8.7% (2 of 23 patients). Thirteen of 23 patients (56.5%) with unexpected and normal variants had neuroimaging findings that would require adjustment in management.

The most common unexpected findings were calcified granulomas (5.3%) and sinus disease (3.5%). The vascular unexpected findings were 2.6% (3 of 114%), neoplastic unexpected findings were 0.9% (1 of 114) and non-neoplastic unexpected findings were 15.8% (18 of 114). Normal variants include 0.9% (1 of 114).

Secondary outcomes:

Male patients were found to have a greater chance of having an unexpected finding or normal variant. The difference in the presence and the absence of nausea and vomiting in normal versus unexpected and normal variant group is significant. More patients in the unexpected and normal variant group did not have nausea and vomiting. (p=0.009). The sharp type headaches were not present in the unexpected and normal variant group and this was also found to be statistically significant (p=0.03), however this was cautiously interpreted as there were large number of poor documentation for this characteristic. There was no association with age and unexpected or normal variant neuroimaging findings. The chances of an unexpected finding or normal variant are almost twice as great in HIV seropositive compared to HIV seronegative patients but did not reach statistical significance.

The cost factor is complex as there are many indirect and direct costs to consider.
If the 91 patients with normal imaging had not been scanned in view of their normal examination, there would have been a saving range of R 169 468 – R 365 196 for the cost of normal scans only.(Supplementary figure 1) This excludes adverse outcomes to contrast (post-contrast related hospital stay, further treatment cost), staff employment costs, machine maintenance costs etc.

Table 1: Patient demographics in all patients and subgroup analysis

Demographics	Subgroup analysis: neuroimaging		Whole cohort (n=114)	p value
	Normal (n=91)	Unexpected and normal variant (n=23)		
Age (years), n (%)				
12 to 30	34 (37.4)	5 (21.7)	39 (34.2)	0.09
31 to 40	23 (25.3)	3 (13.0)	26 (22.8)	
41 to 50	18 (19.8)	11 (47.8)	29 (25.4)	
>50	16 (17.6)	4 (17.4)	20 (17.5)	
Mean Age (mean, SD)	36.84 (14.10)	42.26 (15.88)	37.94 (14.57)	0.12
Male	34.66 (11.78)	35.78 (10.10)	34.92 (11.27)	0.81
Female	37.72 (14.93)	45.72 (17.56)	39.22 (15.65)	0.07
Gender, n (%)				
Male	26 (28.6)	8 (34.8)	34 (29.8)	0.56
Female	65 (71.4)	15 (65.2)	80 (70.2)	
Race, n (%)				
African	39 (42.9)	12 (52.2)	51 (44.7)	0.61
Indian	46 (50.5)	9 (39.1)	55 (48.2)	
Caucasian/ mixed	6 (6.6)	2 (8.7)	8 (7.0)	
Comorbidities, n (%)				
Present	40 (44.0)	13 (56.5)	53 (46.5)	0.28
Absent	51 (56.0)	10 (43.5)	61 (53.5)	
HIV status, n (%)				
Seropositive	4 (4.4)	2 (8.7)	6 (5.3)	0.523

Seronegative	17 (18.7)	5 (21.7)	22 (19.3)	
Unknown	70 (76.9)	16 (69.6)	86 (75.4)	
CT brain, n (%)				
-Contrast	60 (67.4)	12 (66.7)	72 (67.3)	0.95
-Non-contrast	29 (32.6)	6 (33.3)	35 (32.7)	
-Not Applicable	2	5	7	
MRI Brain, n (%)				
-Gadolinium	3 (50.0)	7 (77.8)	10 (66.7)	0.26
-Non-gadolinium	3 (50.0)	2 (22.2)	5 (33.3)	
-Not Applicable	85 excluded	14 excluded	99 excluded	
*Totals do not add up to 100 as figures rounded to one decimal point				

Table 2: Headache characteristics in whole cohort and subgroup with normal versus unexpected findings or normal variant neuroimaging group

	Subgroup analysis: neuroimaging			
Headache characteristics	Normal (n=91)	Unexpected and normal variant (n=23)	Whole cohort (n=114)	p value
Start of headache, n (%)				
< 3months	27 (29.7)	3 (13.0)	30 (26.3)	0.67
3months-1 year	19 (20.9)	10 (43.5)	29 (25.4)	
> 1 year	37 (40.7)	8 (34.8)	45 (39.5)	
NA	8 (8.8)	2 (8.7)	10 (8.8)	
Headache location, n (%)				
Unilateral	21 (23.1)	5 (21.7)	26 (22.8)	0.33
Bilateral	17 (18.7)	4 (17.4)	21 (18.4)	
Holocephalic	14 (15.4)	3 (13.0)	17 (14.9)	
Localised region	37 (40.7)	8 (34.8)	45 (39.5)	
Unknown /not documented	2 (2.2)	3 (13.0)	5 (4.4)	

Onset, n (%)				
Sudden/acute/subacute	22 (24.2)	4 (17.4)	26 (22.8)	0.946
Chronic	5 (5.5)	1 (4.3)	6 (5.3)	
Gradual	8 (8.8)	2 (8.7)	10 (8.8)	
Not documented	56 (61.5)	16 (69.6)	72 (63.2)	
Frequency (per week)				
< 5	26 (28.6)	5 (21.7)	31 (27.2)	0.68
> 5	9 (9.9)	1 (4.3)	10 (8.8)	
Daily/alternate days	37 (40.7)	10 (43.5)	47 (41.2)	
Not documented	19 (20.9)	7 (30.4)	26 (22.8)	
Severity (pain-scale), n (%)				
Mild/moderate	4 (4.4)	1 (4.3)	5 (4.4)	0.052
Severe	39 (42.9)	4 (17.4)	43 (37.7)	
Not documented	48 (52.7)	18 (78.3)	66 (57.9)	
Duration, n (%)				
< 30 min	11 (12.1)	1 (4.3)	12 (10.5)	0.22
30 min-3 hrs	15 (16.5)	4 (17.4)	19 (16.7)	
3hrs - 7 days	28 (30.8)	3 (13.0)	31 (27.2)	
Constant	14 (15.4)	5 (21.7)	19 (16.7)	
Not documented	23 (25.3)	10 (43.5)	33 (28.9)	
Character, n (%)				
Sharp	17 (18.7)	0 (0.0)	17 (14.9)	0.03
Dull/pressure/other	21(23.1)	5 (21.7)	26 (22.8)	
Throbbing	32 (35.2)	7 (30.4)	39 (34.2)	
Not documented	21 (23.1)	11 (47.8)	32 (28.1)	
Constitutional symptoms, n				

(%)				
Present	6 (6.6)	1 (4.3)	7 (6.1)	0.88
Absent	76 (83.5)	21 (91.3)	97 (85.1)	
Not documented	9 (9.9)	1 (4.3)	10 (8.8)	
Nausea and vomiting, n (%)				
Present	36 (39.6)	4 (17.4)	40 (35.1)	0.009
Absent	54 (59.3)	16 (69.6)	70 (61.4)	
Not documented	1 (1.1)	3 (13.0)	4 (3.5)	
Visual disturbance, n (%)				
Present	16 (17.6)	4 (17.4)	20 (17.5)	0.30
Absent	75 (82.4)	18 (78.3)	93 (81.6)	
Not documented	0 (0.0)	1 (4.3)	1 (0.9)	
Photophobia and/or phonophobia, n (%)				
Present	33 (36.3)	9 (39.1)	42 (36.8)	0.81
Absent	58 (63.7)	14 (60.9)	72 (63.2)	
Other features, n (%)				
Present	22 (24.2)	8 (34.8)	30 (26.3)	0.33
Absent	63 (69.2)	14 (60.9)	77 (67.5)	
Not documented	6 (6.6)	1 (4.3)	7 (6.1)	
Autonomic features present, n (%)				
Yes	1 (1.1)	0 (0)	1(0.88)	0.90
No	91 (100)	23 (100.0)	113(99.12)	
Worse with Valsalva, n (%)				
Yes	11 (12.1)	3 (13.0)	14 (12.3)	0.71

No	66 (72.5)	15 (65.2)	81 (71.1)	
Not documented	14 (15.4)	5 (21.7)	19 (16.7)	
Medication response, n (%)				
No response	15 (16.5)	6 (26.1)	21 (18.4)	0.18
Good response	37 (40.7)	9 (39.1)	46 (40.4)	
No medication taken	4 (4.4)	3 (13.0)	7 (6.1)	
Not documented	35 (38.5)	5 (21.7)	40 (35.1)	
*Totals do not add up to 100 as figures rounded to one decimal point				
n - number, HIV – Human Immunodeficiency Virus, min – minutes, hrs – hours,				

Table 3: Subgroup analysis of normal versus unexpected findings or normal variant neuroimaging group

	Subgroup analysis: Neuroimaging		Total	Chances of having unexpected or normal variant on neuroimaging			
	Normal (n=91)	Unexpected and normal variant (n=23)		p value	OR	95% CI	
Gender	n (%)	n (%)	n				
Men	26 (76.5)	8 (23.5)	34		ref	ref	ref
Women	65 (81.3)	15 (18.8)	80	0.56	0.75	0.28	1.98
Age							
<=50	75 (79.8)	19 (20.2)	94		ref	ref	ref
> 50	16 (80.0)	4 (20.0)	20	0.9	0.9	0.30	3.30
HIV status							
Seronegative	17 (77.3)	5 (22.7)	22		ref	ref	ref

Seropositive	4 (66.7)	2 (33.3)	6	0.60	1.70	0.24	12.17
Unknown	70 (81.4)	16 (18.6)	86	0.66	0.78	0.25	2.42
n - number, HIV – Human Immunodeficiency Virus OR: odds ratio; CI: confidence interval, ref: reference							

Discussion

This retrospective chart review study revealed that patients with headaches and a normal clinical examination had unexpected and normal variant neuroimaging findings in 20.2%. The most common unexpected findings were calcified granuloma (5.3%) and sinus disease (3.5%). The vascular unexpected findings were 2.6% (3 of 114%), neoplastic unexpected findings were 0.9% (1 of 114) and non-neoplastic unexpected findings were 15.8% (18 of 114). Normal variants include 0.9% (1 of 114).

This correlated with a systematic review and meta-analysis study by Kamtchum-Tatuene *et al*(20), reviewed 41 studies (15760 patients) revealed a prevalence of unexpected findings or normal variants on brain imaging to be 17.5% in patients with headaches and normal neurologic examination.(20) Sinusitis (8.6%) and white matter abnormalities (7.4%) were the single most prevalent unexpected findings and prevalence of vascular unexpected findings (5.7%) was found to increase with the proportion of migraine patients in the study population and with age.

The findings included vascular, neoplastic, and non-neoplastic changes and prevalence of these findings were 6.6%, 1.4%, and 9.6% respectively. This study concluded that these important findings are rare in patients with headache and normal neurologic examination and are better detected on MRI. The findings supported the recent American and European radiological guidelines. This meta-analysis published in 2020, describes a prevalence of all-type stroke that is nearly 4 times higher in studies with a mean age ≥ 40 years when compared to studies with a mean age < 40 years (3.0% versus 0.8%. As a result, the age of ≥ 40 years should be considered as a red flag in patients with headache, although the difference was not found to be significant.

Clinically significant abnormalities (defined as abnormalities that would change management in patients) and *were* found to be 11.4% (13 of 114) in this study. (See supplementary table 1)

Our study findings were similar to a systematic review and meta-analysis by Jang *et al* which reviewed ten studies, 2377 patients and determined a pooled prevalence of detecting clinically significant abnormalities in headache patients that were neuroimaged to be 8.86% (95% confidence interval: 5.12–15.33%) in primary headache patients. (7) This systemic review included primary headaches, acute severe headache onset and chronic headache onset. In this study (7), a slightly higher prevalence of detecting a significant neurological abnormality was found in the acute onset headache patients compared to the non-acute group. The results also suggest a greater probability of an intracranial abnormality in older patients, specifically patients that are 40 years and older.

In our cohort, patients with the highest percentage of unexpected and normal variants on neuroimaging were in the 41-50 year age range (47.8%) and only 17.4% were above the age of 50 years of age. This is in contrast to traditional red flags which include age over 50.(21) This association did not reach statistical significance; however these differences could be significant in a larger study as demonstrated by meta-analyses. (7, 20) Further statistical analysis was therefore performed and no association between age and unexpected findings or normal variants was found.

A prospective study by Sempere *et al* however detected significant intracranial abnormalities in 0.9% (95% CI 0.5, 1.4) in the same category of patients.(22) The definition of significant abnormalities are lesions that would eventually require surgery or another kind of therapy. The only variable that was associated with increased probability of intracranial abnormality was neurological examination. The study concluded that despite the proportion of patients with headache and intracranial lesions are relatively small, history and neurological examination cannot rule out these abnormalities.

Inclusion of patients with sinus disease in the unexpected neuroimaging group, which accounted for 3.5% (4 of 114), may have contributed to a higher percentage (11.4%) in our study. Sinus disease provided a different cause of headache and resulted in adjustment in management and therefore was included.

.

The difference in the presence and the absence of nausea and vomiting in normal versus unexpected and normal variant group is significant. More patients in the unexpected and normal variant group did not have nausea and vomiting. There is low sensitivity 20% and

high negative predictive value of 77% for this symptom (see supplementary table 2). Nausea and vomiting can be present in primary headaches (predominantly migraines) and when associated with other signs and symptoms (for instance papilloedema, sixth cranial nerve palsy etc.) may indicate a secondary headache. In isolation, nausea and vomiting may not reflect a red flag. The recent red flag list, SNNOOP10 (19), does not include nausea and vomiting as a red flag – therefore our findings correlate well. An older systemic review however recommended neuroimaging for headache with vomiting with a likelihood ratio of 1.8 (95% CI, 1.2-2.6). (23) Our study may largely reflect migraineurs reporting headaches associated with nausea and vomiting.

HIV seropositive patients were included in the study provided they had a normal examination. Two of the 6 patients had unexpected findings on neuroimaging. Although there were many patients whose status was unknown, the chances of having unexpected imaging are almost twice as great in HIV seropositive compared to HIV seronegative patients but did not reach statistical significance. This correlates with studies that deem HIV a red flag as it may reflect an immunosuppressed state.(18)

Patients with features of trigeminal autonomic cephalalgias should be referred to a regional or tertiary centre. MRI brain is usually appropriate for the initial imaging in patients with a new primary headache of suspected trigeminal autonomic origin, as there is an unexplained association with pituitary macroadenomas in 4% of patients.(24) There was one patient in the whole cohort with headaches and autonomic symptoms and this patient was found to have normal neuroimaging.

In addition to trigeminal autonomic cephalalgias, patients experiencing migraine with a change in aura, these patients should be referred for assessment and neuroimaging. These positive visual symptoms may reflect an occipital lobe lesion and will therefore require neuroimaging with an MRI.(25) In this study, the presence of visual disturbance was not statistically significant and did not differentiate the presence, type of aura and change in aura.

Kenteu *et al* highlighted that overuse of neuroimaging may result in frequent discovery of normal variants (NV) which most often do not explain the patient's pain.(26,27) Our study found 1 normal variant (0.9%) in the whole cohort.

The common concerns when encountering a patient with headaches is subarachnoid haemorrhage, aneurysms and tumour. The incidence of subarachnoid haemorrhage (SAH) in patients with sudden severe headache and a normal neurological examination may be as high as 10%.(28) Patients with acute onset headaches, elevated blood pressures, neck stiffness and altered mental state may also prompt further referral. Severity of headaches in our study approached statistical significance however the number of patients with missing data in this category was too high to place any relevance. There were no patients with sharp type headaches found in the unexpected neuroimaging group and this was found to be statistically significant, however there were too many patients for whom this characteristic was not documented and therefore not thought to be relevant.

Cerebral venous thrombosis (CVT) is another life threatening entity that clinicians do not want to miss. A CVT may present with an isolated headache which is thunderclap in nature and should be further investigated with a CT brain. However, CT brain may be normal and an MRI or MR venogram should be performed if clinical suspicion persists.(29) Our cohort did not have any patients with SAH or CVT.

The presence of a brain tumour is one of the greatest concerns for patients with headaches. The risk of a brain tumour increases with age and the presentation with an isolated headache can range between 2% and 16%.(30) Our study revealed one intracranial meningioma which is 0.87% of the whole cohort. A study by Carey *et al* revealed the diagnosis of malignancy was rare in individuals presenting with incident headache and early neuroimaging (within 30 days of headache) lead to a small reduction in time to diagnosis. Interestingly, risk of death was higher in the early neuroimaging group compared to the referent group, and the authors postulate higher disease severity in this group.(31) Therefore timing of neuroimaging did not change outcomes.

The American College of Radiology (ACR) Appropriateness Criteria—Headache Clinical Variants (revised 2019) provides recent evidence-based guidelines on imaging in patients with headaches (21) and advise that initial imaging is usually not appropriate for patients with new primary migraine or tension-type headache with normal neurologic examination, or chronic headache with no new features. However, guidelines for neuroimaging in headaches (2019) by the British Society of Neuroradiologists Standards Subcommittee advise neuroimaging may be considered if a patient is disabled by fear of serious pathology.(32)

Strengths of our study included data collected from a centre with an electronic database. The data collection was done by one author and reduced the interpretation bias. Neuroimaging was done at a single location and this ensured uniformity in reporting and image acquisition protocols and ease of report access. Clinical assessments for this study were only considered from the neurology clinic, again ensuring consistency in history taking and clinical examination.

Limitations include retrospective design, and as a result missing data and risk of bias when interpreting data. The HIV status of most patients was unknown and may reflect a time when HIV testing in South Africa was not well established in all regions. This study offers insights into neuroimaging in patients with a normal neurological examination at a single centre, however generalizability is limited. The study is also subject to referral bias, as it was conducted at a tertiary referral centre. This can overestimate or underestimate the rate of intracranial abnormalities.

To our knowledge, this is the first study of this nature in South Africa and Africa to correlate the neuroimaging findings of patients with headaches and normal clinical examination. These findings have far reaching implications for practitioners involved in the management of patients in this category.

Further prospective studies are recommended to assess yield of unexpected findings in patients with neuroimaging both in the emergency department and Neurology departments. Characteristics such as age (40 years and older), nausea, vomiting and nature of headache should be further explored. This will contribute to locally developed guidelines based on resource availability and combination HIV related population.

Patients should be included in the decision making process and counselled with regards to the benefits, harm and timing of neuroimaging. Defensive medicine may be reduced if clinicians are shielded by law when practicing evidence-based medicine in accordance with published guidelines.(33) The practitioner plays an important role in the initial clinical assessment as serious illness can be detected despite normal imaging.(34) Further, a normal investigation does not eliminate the need for further follow up and appropriate management of headache.

Conclusion:

We advise embracing a lower threshold to image patients that are male, HIV seropositive patients, patients in the 41-50 year age group. Importantly, this study demonstrates that headache with nausea and vomiting in isolation, may be associated with normal neuroimaging reflecting primary type headaches. In patients with primary headaches and a normal neurological examination, we advise referral of a subgroup of patients with trigeminal autonomic cephalalgias and migraine with change in aura

Acknowledgments: Thanks to Catherine Connolly for biostatistical input and to Dr K. Kistan for additional guidance.

Supplementary data

Supplementary data Table 1: Unexpected and normal variants Neuroimaging findings

Unexpected and normal variants Neuroimaging findings	Number	Classification: Normal variant(NV) and unexpected findings (UF)	Change in management
Calcified granuloma	6	UF	No
Sinus disease	4	UF	Yes
Basal ganglia calcification	2	UF	No
Multiple rim-enhancing lesion	2	UF	Yes
Ischaemic leukoencephalopathy	1	UF	Yes
Basal ganglia infarct	1	UF	Yes
Vascular anomaly- pons nidus of vessels	1	UF	Yes
Atrophy of the parietal lobe	1	UF	No
Rathke cyst	1	UF	Yes
Meningioma	1	UF	Yes
Asymmetry of the lateral ventricles	1	NV	No
Supratentorial Hydrocephalus	1	UF	Yes
Enhancing rounded lesions are noted in left head of caudate nucleus and within the pons centrally	1	UF	Yes
Total	23	NV: 1 UF: 22	No = 10, Yes = 13

Supplementary data Table 2: Nausea and vomiting – sensitivity and specificity findings

	Unexpected and normal variant neuroimaging findings	Normal neuroimaging	Total
Present	4	36	40
Absent	16	54	70
Total	20	90	110

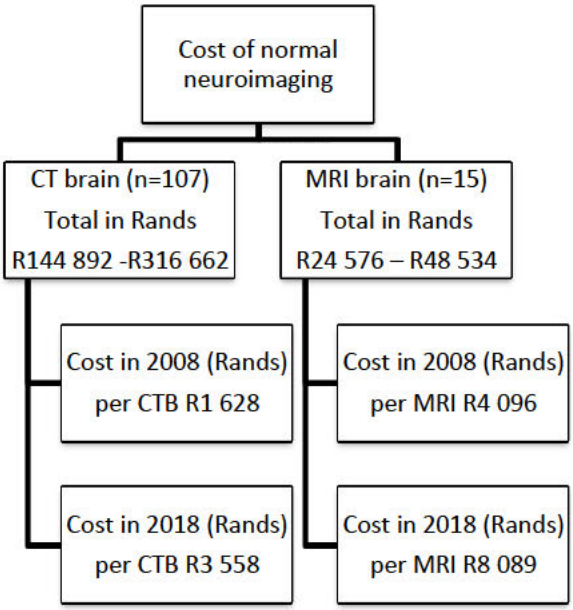
Sensitivity: 0.2 = 20%

Specificity: 0.6 =60%

Negative Predictive value: 0.77= 77%

Positive predictive value: 0.1 = 10%

Supplementary figure 1: Cost of normal neuroimaging (R=South African Rands)



References

1. Rizzoli P, Mullally WJ. Headache. Am J Med. 2018;131(1):17-24. https://doi.org/10.1212/01.wnl.0000072526.35698.0a

2. WHO. Headache disorders: World Health Organization; 2016(updated April 2016; cited 2017 6th October). 2016 http://www. who.int/ mediacentre/ factsheets/ fs277/ en/. https://www.who.int/news-room/fact-sheets/detail/headache-disorders

3. Safiri S, Pourfathi H, Eagan A, Mansournia MA, Khodayari MT, Sullman MJM, *et al*. Global, regional, and national burden of migraine in 204 countries and territories, 1990 to 2019. PAIN. 9000. https://doi.org/10.1097/j.pain.0000000000002275

4. Goldberg LD. The cost of migraine and its treatment. Am J Manag Care. 2005;11(2 Suppl):S62-7. https://pubmed.ncbi.nlm.nih.gov/16095269/

5. Steiner TJ, Scher AI, Stewart WF, Kolodner K, Liberman J, Lipton RB. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia. 2003;23(7):519-27. https://doi.org/10.1046/j.1468-2982.2003.00568.x

6. Saylor D, Steiner TJ. The Global Burden of Headache. Semin Neurol. 2018;38(2):182-90. https://doi.org/10.1055/s-0038-1646946

7. Jang YE, Cho EY, Choi HY, Kim SM, Park HY. Diagnostic Neuroimaging in Headache Patients: A Systematic Review and Meta-Analysis. Psychiatry investigation. 2019;16(6):407-17. https://dx.doi.org/10.30773%2Fpi.2019.04.11

8. Holle D, Obermann M. The role of neuroimaging in the diagnosis of headache disorders. Ther Adv Neurol Disord. 2013;6(6):369-74. https://doi.org/10.1177/1756285613489765

9. Evans RW. Diagnostic testing for headache. Med Clin North Am. 2001;85(4):865-85. https://doi.org/10.1016/s0025-7125(05)70348-5

10. Callaghan BC, Kerber KA, Pace RJ, Skolarus LE, Burke JF. Headaches and neuroimaging: high utilization and costs despite guidelines. JAMA internal medicine. 2014;174(5):819-21. https://doi.org/10.1001/jamainternmed.2014.173

11. Sandrini G, Friberg L, Jänig W, Jensen R, Russell D, Sanchez del Rìo M, *et al*. Neurophysiological tests and neuroimaging procedures in non-acute headache: guidelines and

recommendations. Eur J Neurol. 2004;11(4):217-24. https://doi.org/10.1111/j.1468-1331.2010.03212.x

12. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. https://doi.org/10.1177/0333102417738202

13. Kenteu B, Fogang YF, Nyaga UF, Zafack JG, Noubiap JJ, Kamtchum-Tatuene J. Neuroimaging of headaches in patients with normal neurological examination: protocol for a systematic review. BMJ Open. 2018;8(2):e020190. https://dx.doi.org/10.1136%2Fbmjopen-2017-020190

14. Callaghan BC, Kerber KA, Pace RJ, Skolarus L, Cooper W, Burke JF. Headache neuroimaging: Routine testing when guidelines recommend against them. Cephalalgia. 2015;35(13):1144-52. https://doi.org/10.1177/0333102415572918

15. Fouche PE, Jenkins LS, Vermeulen A. Appropriateness of computed tomography and magnetic resonance imaging scans in a rural regional hospital in South Africa: A 6-year follow-up study. S Afr Med J. 2020;111(1):46-51. https://doi.org/10.7196/samj.2020.v111i1.14860

16. Elliott P, Ku NN, Werner MH. Neoplastic meningitis with normal neurological findings. Magnetic resonance imaging results. J Neuroimaging. 1995;5(4):233-6. https://doi.org/10.1111/jon199554233

17. Rozen TD. A New Subtype of Chronic Daily Headache Presenting in Older Women. J Womens Health (Larchmt). 2018;27(2):203-8. https://doi.org/10.1089/jwh.2017.6460

18. Lee VME, Ang LL, Soon DTL, Ong JJY, Loh VWK. The adult patient with headache. Singapore medical journal. 2018;59(8):399-406. https://doi.org/10.11622/smedj.2018094

19. Do TP, Remmers A, Schytz HW, Schankin C, Nelson SE, Obermann M, *et al*. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. Neurology. 2019;92(3):134-44. https://doi.org/10.1212/wnl.0000000000006697

20. Kamtchum-Tatuene J, Kenteu B, Fogang YF, Zafack JG, Nyaga UF, Noubiap JJ. Neuroimaging findings in headache with normal neurologic examination: Systematic review and meta-analysis. J Neurol Sci. 2020;416:116997. https://doi.org/10.1016/j.jns.2020.116997

21. Whitehead MT, Cardenas AM, Corey AS, Policeni B, Burns J, Chakraborty S, *et al*. ACR Appropriateness Criteria® Headache. J Am Coll Radiol. 2019;16(11s):S364-s77. https://doi.org/10.1016/j.jacr.2019.05.030

22. Sempere AP, Porta-Etessam J, Medrano V, Garcia-Morales I, Concepción L, Ramos A, *et al*. Neuroimaging in the evaluation of patients with non-acute headache. Cephalalgia. 2005;25(1):30-5. https://doi.org/10.1111/j.1468-2982.2004.00798.x

23. Detsky ME, McDonald DR, Baerlocher MO, Tomlinson GA, McCrory DC, Booth CM. Does this patient with headache have a migraine or need neuroimaging? Jama. 2006;296(10):1274-83. https://doi.org/10.1001/jama.296.10.1274

24. Levy MJ, Matharu MS, Meeran K, Powell M, Goadsby PJ. The clinical characteristics of headache in patients with pituitary tumours. Brain. 2005;128(Pt 8):1921-30. https://doi.org/10.1093/brain/awh525

25. Micieli A, Kingston W. An Approach to Identifying Headache Patients That Require Neuroimaging. Frontiers in public health. 2019;7:52. https://doi.org/10.3389/fpubh.2019.00052

26. Valenca MM, Valenca LP, Menezes TL. Computed tomography scan of the head in patients with migraine or tension-type headache. Arq Neuropsiquiatr. 2002;60(3-A):542-7. https://pubmed.ncbi.nlm.nih.gov/12244387/

27. Evans RW. Incidental Findings and Normal Anatomical Variants on MRI of the Brain in Adults for Primary Headaches. Headache. 2017;57(5):780-91. https://doi.org/10.1111/head.13057

28. Cooper JG, Smith B, Hassan TB. A retrospective review of sudden onset severe headache and subarachnoid haemorrhage on the clinical decision unit: looking for a needle in a haystack? Eur J Emerg Med. 2016;23(5):356-62. https://doi.org/10.1097/mej.0000000000000266

29. Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. Journal of Neurology, Neurosurgery & Psychiatry. 2005;76(8):1084-7. https://doi.org/10.1136/jnnp.2004.056275

30. Kernick DP, Ahmed F, Bahra A, Dowson A, Elrington G, Fontebasso M, *et al*. Imaging patients with suspected brain tumour: guidance for primary care. Br J Gen Pract. 2008;58(557):880-5. https://dx.doi.org/10.3399%2Fbjgp08X376203

31. Carey MR, Callaghan BC, Kerber KA, Skolarus LE, Burke JF. Impact of early headache neuroimaging on time to malignant brain tumor diagnosis: A retrospective cohort study. PLoS One. 2019;14(2):e0211599. https://dx.doi.org/10.1371%2Fjournal.pone.0211599

32. Headache Consortium. Evidence-based guidelines in the primary care setting: neuroimaging in patients with nonacute headache. [cited 16 Oct 2008]. Available from url:http://www.americanheadachesociety.org/professionalresources/USHeadacheConsortium Guide lines.asp)

33. Jordan JE, Flanders AE. Headache and Neuroimaging: Why We Continue to Do It. AJNR Am J Neuroradiol. 2020;41(7):1149-55. https://doi.org/10.3174/ajnr.a6591

34. Neuroimaging for the evaluation of chronic headaches: an evidence-based analysis. Ont Health Technol Assess Ser. 2010;10(26):1-57. Epub 2010 Dec 1. PMID: 23074404; PMCID: PMC3377587 http://www.ncbi.nlm.nih.gov/pmc/articles/pmc3377587/

Appendices

Appendix 1: List of abbreviations and definitions

CT	Computed tomography
CSF	Cerebrospinal fluid
CVT	Cerebral venous thrombosis
DALYs	Disability-adjusted life years
HIV	Human Immunodeficiency Virus
IALCH	Inkosi Albert Luthuli Central Hospital
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiogram
MRV	Magnetic resonance venogram
TTH	Tension Type Headache
WHO	World Health Organisation
YLD	years lived with disability

Definitions

1. Normal variants: anatomical variants that do not have the potential to cause symptoms and do not need any therapeutic intervention.
2. Unexpected findings: were defined as any neuroimaging finding distinct from known and well-characterized normal variants, irrespective of the potential relationship with the headache or the subsequent management (in the context of a normal neurologic examination)
3. Significant abnormalities on neuroimaging (according to Sempere *et al*(22)): neoplastic disease, hydrocephalus, vascular malformations, Chiari malformation, large arachnoid cysts, intracranial haemorrhage, and acute cerebral infarcts. Defined as lesions that would eventually require surgery or another kind of therapy.

Appendix 2: BREC protocol

PROTOCOL NUMBER:

.....

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

BIOMEDICAL RESEARCH ETHICS COMMITTEE
EXPEDITED APPLICATION FORM

Application to the UKZN Research Ethics Committee for ethics review of new research projects

For office use only

(For research on human participants)

RESEARCH OFFICE CONTACT DETAILS: Biomedical Research Ethics Administration, Westville Campus, Govan Mbeki Building, Private Bag X 54001, Durban, 4000,
KwaZulu-Natal, South Africa; Tel: +27 31 2602486; Email: BREC@ukzn ac za ; Website: http://research ukzn ac za/Research-Ethics/Biomedical-Research-Ethics aspx

SECTION A:

APPLICANT/PRINCIPAL INVESTIGATOR: * *For UKZN statistical reporting purposes*

Title:	Mr		Ms		Mrs		Dr	X	Prof		*(Select option)*

Name :	Sharania Moodley		
*Gender:female			
*Race: Indian			
UKZN College: Nelson R Mandela School of Medicine			
UKZN School/Discipline:	SCM/Neurology	NA	
Hospital/Institution where employed:	Inkosi Albert Luthuli Central Hospital	NA	
Professional status:	Neurology Registrar		
Postal address:	P.O. BOX 1650, Westville, 3630		
Contact phone Numbers: Office:	031 240 2359		
Mobile number:	0731634116		
Fax number:	031-2402358		
Email address:	206501362@stu.ukzn.ac.za sharmoodley@gmail.com		
Full/Part time Employment: Department of Health Full time			
Current HPCSA Number (or equivalent): MP 0730009 *if registration is pending, submit proof of application			

Purpose of research: If postgraduate degree *(Please tick)*	Hons	MMedSc	MMed √	MSc	MFamMed	MChB	PhD	N/A
Other degree not listed above: No								
Student Number and year of study: (*if applicable)* 206501362, year [1]								
If for postgraduate degree, please confirm whether the application has been reviewed and approved by your school's Academic Leader (Research):	Yes	X	No					

If yes, provide approval date and attach approval letter:
Title of research project: **The association between headache presentation, clinical examination and radiological findings: A retrospective analysis of patients presenting to a tertiary referral centre**
Name and qualifications of Supervisor: A I BHIGJEE. PhD, MRCP e-mail address of Supervisor: Bhigjee@ukzn.ac.za
Name and qualifications of Co-supervisor: N/A e-mail address of co-supervisor: N/A
If not for degree purposes, state other (example, self-initiated research): N/A

Has this study been, or is it likely to be, submitted to any other Research Ethics Committee?	Yes		No	X	N/A	

If yes, please name the Committee/s and or institution and give outcome - i.e. approved/rejected/pending/not applicable? *(If approved, attach approval letter)* N/A
Please state number of Co-investigators in project:[2] **(if additional space is required for more investigators details please add to the end of application)**
CO-INVESTIGATOR/S ROLE IN PROJECT ** For UKZN statistical reporting purposes*
Name: N/A
Faculty:
Department:
*Gender:
*Race:
Role:
e-mail address:
Signature of Co-Investigator:
Name:
Faculty:
Department:
*Gender:

[1] Note: This application must be self-sufficient. Sections marked "see protocol" are unacceptable and will be returned to the applicant.

[2] Please note that because of conflict of roles and interests that can arise, academic supervisors and coinvestigators should be separate individuals.

*Race:
Role:
e-mail address:
Signature of Co-Investigator:
Name:
Faculty:
Department:
*Gender:
*Race:

Role:				
e-mail address:				
Signature of Co-Investigator:				
Has the Principal Investigator or any of the co-investigators been previously/or are presently being investigated for alleged research misconduct? *(If yes, please provide details and dates)*	Yes		No	X
FUNDING OF THE RESEARCH:				
Has funding been secured? N/A	Yes		No	X
Amount: R				
Name of funder: *(full details)*				
Is this project funded from a US DHHS funding source?	Yes		No	X
If yes, name the federal funding agency:				
Can this project proceed without funding? *(give a brief explanation)* **This is a retrospective descriptive study**	Yes	X	No	
Has an application for funds been made to other sources to support this project?	Yes		No	X
If yes, state name/s of funding agency and amount requested: N/A				

Note:

For all US Federally funded studies (e.g. NIH, CDC, NIAID, DAIDS, NIMH, etc), one complete copy of the original funding application and approval must accompany the BREC ethics application.

All University contracts need to be uploaded on the Contracts Management online submission form with either the signed **Approval letter** (non-research) **or Form 1**(research related). The website link to the system is http://legalservices.ukzn.ac.za/ContractsManagement.aspx

If you require assistance with the completion of the online submission form, or with any aspect of the new system, please contact Mr Rendra Phalad on Ext 7455 for all contracts (non-research contracts), and Mr Deon Moodley on Ext 8199 (for research contracts).

FAILURE TO MAKE FULL FINANCIAL DISCLOSURES WILL DELAY ETHICS APPROVAL

Please indicate whether a BREC review fee is applicable for this study? (See Fee Schedule on BREC Website)	Yes		No	X
If Yes, is the study covered by your Centre/Unit's annual levy fee to BREC? N/A	Yes		No	

Note:

* Expedited review only applies to minimal risk studies – e.g. retrospective chart reviews, studies on stored samples etc., for details see BREC ToR and SoP at *http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx*

SECTION B:

NATURE OF STUDY

Quantitative					
Type of Study: *(please tick)*	Epidemiological	Observational clinical study	Experimental	Observational	
	Retrospective Chart Review X	Prospective Chart Review	Laboratory study on stored samples	Audit	Other:(Specify)

Qualitative

1. THE PROTOCOL FOR STUDY

1.1 Full title of research project: *(Please DO NOT use abbreviations or acronyms)*

The association between headache presentation, clinical examination and radiological findings: A retrospective analysis of patients presenting to a tertiary referral centre

1.2 Where will the Research be carried out? (Hospital, clinic etc.). Inkosi Albert Luthuli Central Hospital

1.3 Aims (what you hope to achieve) and objectives (how you will achieve your aims) of study: *(please list)*

The aim of this study is to determine the spectrum of neuroimaging findings in patients with headaches and a normal clinical examination.

Primary objectives

- To determine the number of patients presenting with a headache, a normal clinical examination and abnormal imaging and if the abnormal findings are clinically relevant.

Secondary objective

- To identify red flags
- To determine an estimate cost to the state sector following further analysis of the scans.

1.4 Hypothesis to be tested, or Research Question to be answered:

Most patients with a main complaint of headaches will have normal neuro-imaging if the clinical examination is normal.

1.5 Summary of the proposed research methodology (restrict to 100 words)

This is a descriptive retrospective analysis of patients presenting to a tertiary referral centre (Inkosi Albert Luthuli Central Hospital) with headaches and a normal clinical examination. Data will be analysed from January 2008 to January 2018. This will be undertaken by chart review. Data collection will include an Excel spreadsheet with patient demographics, co-morbidities including Human Immunodeficiency Virus (HIV), neuroimaging findings and headache characteristics. Cost to state will be calculated based on the number of scans that could have been avoided in the selected population.

1.6 Keywords (for database):
Headache, Normal examination, Neuro-imaging

1.7 Background and Literature Review (maximum 1 page):

Headache disorders are a global public health burden and have an estimated prevalence of 50% as described by the World Health Organisation.(1) This results in disability, medication overuse and increased cost to society. Headache disorders can be classified into primary headache disorders, resulting from the headache condition itself and secondary headaches which are due to other conditions causing pain. Primary headache disorders are the most common type of headache disorder. (1)
Since imaging of all patients with headache is not feasible, it is essential to know which category of patients to image. Kenteu et al recently published a protocol focused on the prevalence of incidental findings and normal anatomic variants on neuroimaging studies performed in patients presenting with headache and normal neurological examination based on a systematic review. (1)

The diagnosis of headache disorders is largely based on history and clinical examination. Neuroimaging may be performed in this setting to exclude a treatable lesion like an intracranial tumour or vascular malformation and sometimes also to reassure the patient.(2) Medico-legal claims and requests by patients may also result in performing of brain imaging.(2) This results in overuse of neuroimaging and frequent discovery of normal variants or incidental findings.
Patients with acute onset headaches and normal clinical examination will require serious secondary causes like subarachnoid haemorrhage (SAH) to be excluded as prompt management is imperative.(3) The incidence of SAH in patients with sudden severe headache and a normal neurological examination may be as high as 10%.(3) A study by Alons et al, revealed a high number of vascular abnormalities despite normal neurological examination and normal computer tomography (CT) findings and cerebrospinal fluid (CSF) results.(4) Alons et al further performed a metaanalysis which revealed a low diagnostic yield of CT angiogram in the setting of an acute headache, normal neurological examination and normal non-contrast CT and demonstrated that the number needed to scan to find an abnormality as 14.(5)

An article published by Kernick et al, approached imaging patients with a possible brain tumour by identifying the incidence of patients with brain tumour and then further determined that 72 percent of this category are over the age of 50.(6) They further divided the risk of brain tumour into red, orange and yellow flags and suggested management accordingly. This article also briefly described the benefits of imaging (patient and doctor reassurance from exclusion of serious pathology) and the disadvantages of imaging (identification of incidental findings and associated anxiety, implications on future insurance applications, effects of radiation from CT scanning, contrast nephropathy and discomfort of MRI scans).

The American college of Radiology appropriateness criteria recognised the social benefit in negative imaging studies in the setting of headache as the headaches symptoms and anxiety itself may affect quality of life and productivity. Other rare causes of a headache and normal examination are found in patients with systemic malignancy and resultant neoplastic meningitis(7) and recently chronic daily headaches have been described in menopausal or perimenopausal patients.(8)
Patients with classic migraine or tension type headache do not require neuroimaging as part of their work up as these patients do not have a higher rate of relevant cerebral pathology when compared to the general population.(9)

Headaches are a common neurological complaint in patients. It is impractical to investigate all cases of headaches with a normal neurological examination. The study to be undertaken should identify ‘red flags’ on assessment of history and determine the yield of neuroimaging.

1.8 Key References:

(Give approximately 5 key references)

1. Kenteu B, Fogang YF, Nyaga UF, Zafack JG, Noubiap JJ, Kamtchum-Tatuene J. Neuroimaging of headaches in patients with normal neurological examination: protocol for a systematic review. BMJ Open. 2018;8(2):e020190.

2. Sempere AP, Porta-Etessam J, Medrano V, Garcia-Morales I, Concepcion L, Ramos A, et al. Neuroimaging in the evaluation of patients with non-acute headache. Cephalalgia. 2005;25(1):30-5.

3. Cooper JG, Smith B, Hassan TB. A retrospective review of sudden onset severe headache and subarachnoid haemorrhage on the clinical decision unit: looking for a needle in a haystack? Eur J Emerg Med. 2016;23(5):356-62.

4. Alons IM, van den Wijngaard IR, Verheul RJ, Lycklama a Nijeholt G, Wermer MJ, Algra A, et al. The value of CT angiography in patients with acute severe headache. Acta Neurol Scand. 2015;131(3):164-8.

5. Alons IME, Goudsmit BFJ, Jellema K, van Walderveen MAA, Wermer MJH, Algra A. Yield of Computed Tomography (CT) Angiography in Patients with Acute Headache, Normal Neurological Examination, and Normal Non Contrast CT: A Meta-Analysis. J Stroke Cerebrovasc Dis. 2018;27(4):1077-84.

6. Kernick DP, Ahmed F, Bahra A, Dowson A, Elrington G, Fontebasso M, et al. Imaging patients with suspected brain tumour: guidance for primary care. Br J Gen Pract. 2008;58(557):880-5.

7. Elliott P, Ku NN, Werner MH. Neoplastic meningitis with normal neurological findings. Magnetic resonance imaging results. J Neuroimaging. 1995;5(4):233-6.

8. Rozen TD. A New Subtype of Chronic Daily Headache Presenting in Older Women. J Womens Health (Larchmt). 2018;27(2):203-8.

9. Holle D, Obermann M. The role of neuroimaging in the diagnosis of headache disorders. Ther Adv Neurol Disord. 2013;6(6):369-74.

2. PLAN OF INVESTIGATION FOR STUDY

* In the case of Higher Degrees, please state name and School of person consulted regarding the design:

2.1 Is this a retrospective chart review with no human contact?	Yes	X	No	
2.2 Is this a study of stored tissue?	Yes		No	X
2.3 Are host genetic factors being studied?	Yes		No	X

2.4 How many hours per week will the PI devote to this project?
(Timetable the project in terms of the resources and time available) 5 hours per week

2.5 Describe in detail your data collection methods for the research project

Hospital permission will be obtained prior to data collection. Adult patients with main complaint of headaches will be identified using the ICD coding system. Further information regarding demographics, headache characteristics and radiological findings will be extracted and analysed. Patients will be given a unique number to maintain anonymity

3. STATISTICAL PLANNING AND DATA ANALYSIS

3.1 Has this project been approved by a professional statistician? Yes No If No, please justify.		X		

3.2 If answered "yes" to (3.1), provide the name of the statistician:
Catherine Connolly

3.3 Please provide a brief overview of statistical and data analytic considerations, including:
How was the number of participants determined? Please include assumptions made in any power analysis (e.g. control incidence or mean and standard deviation of primary outcome variable, desired or anticipated effect of treatment or intervention, level of statistical significance and desired power), and list all planned statistical methods to be used. For descriptive studies list statistical operations to be performed.

A sample of 114 patients presenting with headache and normal clinical findings is required to estimate the proportion of patients with abnormal neuroimaging findings to within ± 13% (37% - 63%) with probability of 95% and assuming an uninformed percentage of 50%. Sample size was estimated using Stata V13.1.

Statistical analysis

Descriptive statistics on the demographic and clinical characteristics of patients will be reported. Factors associated with abnormal neuroimaging (red flags) will be identified using Chi Square tests for categorical variables and analysis of variance/t test or Wilcoxon rank sum tests/Kruskal Wallis for numeric variables depending on their distribution. To identify independent factors and adjust for possible confounding variables significant at the $p < 0.3$ at the bivariate level will be included in a logistic regression model. The number of variables included will depend on the prevalence of the outcome. Backwards elimination will be used to identify independent factors significant at $p < 0.05$. Both unadjusted and adjusted odds ratios and 95% confidence limits will be reported. Post-hoc testing of the model will be done using linktest for model specification; Hosmer-Lemeshow for model fit and Lowess smoother to confirm linearity. Data will be analysed using Stata Statistical software V13.1

3.4 For *qualitative* studies: What is the framework/approach to be used for analysis of the data? N/A

4. PARTICIPANTS IN THE STUDY

4.1 Is this a multi-national study? (*If yes, state collaborating countries)*	Yes			No	X	

4.2 List all sites in South Africa in which the project will be carried i.e. geographic location (e.g. KwaZulu-Natal) and type of place (e.g. hospital, clinic, schools, community etc).

KwaZulu Natal, Durban, Mayville, Inkosi Albert Luthuli Central Hospital

4.3 Source: *(Please indicate number per group)*	Inpatients	Outpatients	Volunteers
		X	

4.4 Age (human studies) *(Please indicate number per group)*	Neonates (<28 days)	Infants (1-11 month)	Children (1-12 years)	Adolescent (13-17 years)	Adults
			X	X	X

4.5 Is there a control group(s)?	Yes		No	X	

4.6 Demographic profile of participants *(please tick ALL appropriate boxes below.)*

4.6.1 Gender: Female [X] Male [X]

4.6.2 Population Group: Black [X] Coloured [X] Indian [X] White [X]

4.6.3 Language Group/s: Specify……
English, isiZulu, Afrikaans

4.7 Describe the recruitment process in detail for all groups.
Retrospective chart review, therefore recruitment not required

4.8 Will incentives be offered to facilitate recruitment? (*If yes, describe in detail*)	Yes		No		N/A	X
4.9 Will participants be reimbursed in some way for participation? (*If yes, describe in detail*) *See SA DoH Guidelines on BREC Website*	Yes		No		N/A	X
4.10 Will reimbursement for participants and investigators be in accordance with: *(If no, please explain)* • Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa: Department of Health (2006) and; • Ethics in Health Research: Principles, Structures and Processes: (2015) • Current SA DoH Guidance on reimbursement (*See BREC website*)	Yes		No		N/A	X
4.11 Will participants be insured against research related injury? *(If yes, please provide details; If no, please provide rationale)* *Mandatory for Clinical Trials*	Yes		No		N/A	X

4.12 List in detail the inclusion and exclusion criteria.

Inclusion criteria

- Presenting complaint of headaches and a normal neurological examination
- Patients that have MRI and CT brain scans and reported by Radiologist
- Patients will be selected from outpatient Neurology clinic
- Children of the age of 12 years and older

Exclusion criteria

- Patients with a history of cranial vault or central nervous system pathology
- Duplicate patient files under 2 different hospital numbers: the older file/ file with the least data will be excluded
- Patients with falls or trauma related injuries
- Patients less that the age of 12
- Patients that have not undergone Neuroimaging at Inkosi Albert Luthuli hospital
- No neuroimaging report available
- Post procedural headaches
- Pregnant patients with new onset headaches
- Patient has not been assessed by a Neurology doctor

5. POTENTIAL RISKS OR DISCOMFORT						
5.1 Can the project have any potential risks or discomfort on participants, members of the public, researchers, field staff or the physical environment?	Yes		No	X		

5.2 If "yes" to (6.1) indicate, for each study group/arm, the potential additional risks as follows:
5.2.1 Biological risks
5.2.2 Psychological risks
5.2.3 Social Risks
5.2.4 Legal risks
5.2.5 Financial risks
5.2.6 Other risks

5.3 Please detail steps that will be taken to minimise the risks indicated above:
5.3.1 Biological risks
5.3.2 Psychological risks
5.3.3 Social Risks
5.3.4 Legal risks
5.3.5 Financial risks
5.3.6 Other risks

6. INFORMED CONSENT: GIVEN TO PARTICIPANTS

See SAMPLE INFORMATION SHEET AND CONSENT FORM ON UKZN BREC WEBSITE at *http://research.ukzn.ac.za/Libraries/Notices2011/BREC_Informed_consent_form_sflb.sflb.ashx*

Other consent forms are acceptable provided that they contain at least the essential elements outlined in the current UKZN BREC Terms of Reference (ToR) and Standard Operating Procedures (SoP) available at *http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx*

If necessary, information sheets and consent forms, after ethics approval of the English version, must be translated into appropriate local languages and submitted to BREC for further approval prior to implementation, with a copy of the translator's certificate, and back translations if applicable.

The correct and complete contact details for the UKZN Biomedical Research Ethics Committee should be in the information sheets and consent forms as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
University of KwaZulu-Natal
Private Bag X 54001, Durban, 4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2602486 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

7. DECLARATION OF PRINCIPAL INVESTIGATOR

Conflict of Interest:

I declare that all potential conflicts of interest regarding my application for ethics approval to conduct this study have been declared in accordance with UKZN and BREC Terms of Reference and Standard Operating Procedures.

Undertaking:

I understand and accept that I will be required to submit a yearly recertification application, failing which authorisation to continue the study lapses.
I undertake to request permission for any changes/amendments to the study from BREC in advance of implementing any such changes, unless they are emergencies required to prevent harm or save life. In such cases BREC must be notified urgently.

I agree to provide monitoring data if and when required.

I expect the project to be completed by **DATE**……01/07/2019……

I agree to abide by the guidance contained in the SA Department of Health (2015) Ethics in Health Research: Principles, structures and processes and the (2006) South African Good Clinical Practice Guidelines and the current UKZN Biomedical Research Ethics Committee Terms of Reference and Standard Operating Procedures. These are available at *http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx*

I understand and accept that all information pertaining to this application is a true reflection of the project proposed and I take full responsibility should there be any transgression.

SIGNATURE OF PRINCIPAL INVESTIGATOR……[redacted]……

FULL NAME OF PRINCIPAL INVESTIGATOR…Sharania Moodley……

DATE……26/01/2019……..

8. DECLARATION AND APPROVAL FROM SUPERVISOR AND CO-SUPERVISOR (if applicable)

(I HAVE READ AND CHECKED THE PROPOSAL AND IT IS READY FOR SUBMISSION;

Remarks:

SIGNATURE OF SUPERVISOR ……..…… [redacted] ……

FULL NAME OF SUPERVISOR… Ahmed Iqbal Bhigjee……

DATE……26/01/2019……..

SIGNATURE OF CO-SUPERVISOR ……..……

FULL NAME OF CO-SUPERVISOR…..……

DATE……..

If applicable, attach a signed copy of the Supervision Agreement between the student, supervisor and any cosupervisor.

9. DECLARATION AND APPROVAL OF LINE MANAGER/HOD/ACADEMIC LEADER
(Must include verification of interdepartmental agreements and co-operation)

Remarks:

SIGNATURE OF ACADEMIC LEADER/HOD OR LINE MANAGER ……  ……
……

FULL NAME OF ACADEMIC LEADER/HOD OR LINE MANAGER…… Ahmed Iqbal Bhigjee……

DATE……26/01/2019……..

NB: If applicant is ACADEMIC LEADER/DEAN/HOS, the ACADEMIC LEADER'S/DEAN'S/HOS's Line Manager (DVC) must sign.

SIGNATURE OF ACADEMIC LEADER's/ HOS's/DEAN's Line Manager……

FULL NAME OF ACADEMIC LEADER's, HOS's/DEAN's Line Manager……

DATE……..

SUGGESTED CURRICULUM VITAE FORMAT

(3 COPIES MAXIMUM 4 PAGES)

CURRICULUM VITAE (of Principal Investigator and all Co-Investigators)
(CVs to be completed and signed for each member of the research team)

Full name: Sharania Moodley
Date of birth: 06/07/1987
Male/Female: female
Telephone (Home): 073 163 4116
Telephone (Business): 073 163 4116
Cell: 073 163 4116
Fax No: 031240 2358
E-mail Address: sharmoodley@gmail.com
Current HPCSA No: MP 0730009
Present position: Neurology registrar
Institution: Inkosi Albert Luthuli Central Hospital Department/Section:
Neurology
Nationality/Permanent residency: South African

Previous positions held (last 10 years):

Date	Job title	Institution
01 Jan 2018-current	Neurology registrar	Inkosi Albert Luthuli Central hospital
01 Jun 2017-31 Dec 2017	Neurology Medical officer	Inkosi Albert Luthuli Central hospital
01 Jan 2014-31 May 2016	Family medicine Medical Officer	King Dinuzulu Hospital
01 Jan 2013-31 Dec 2013	Community Service Medical Officer	KwaMashu Polyclinic
01 Jan 2011-31 Dec 2012	Medical Intern	Pietermaritzburg Metropolitan Hospital complex

Qualifications:
MBChB,
DipPEC(SA)
University where obtained/year:
MBChB – University of KwaZulu Natal 2010
DipPEC (SA) – College of Medicine South Africa 2014

Area of study: Neurology

Number of Postgraduate theses supervised (Masters and Doctoral): 0 Publication list over the past 3 years: 0

Details of all other research studies presently being conducted:

1. The relationship of the cause and effect between venous sinus stenosis and Benign intracranial hypertension

2. The use of corneal confocal microscopy as a surrogate non-invasive tool for the assessment of small fibre neuropathy in HIV positive individuals

Certificate of recent (past 3 years) research ethics and/or GCP training (GCP required for clinical trials): Completed and attached

Signature of PI/Co-PI:

……..

CHECKLIST FOR BIOMEDICAL RESEARCH ETHICS APPLICATIONS NB: DO NOT BIND SUBMISSIONS (STAPLE ONLY)

Applications to be addressed to: The Administrator, Biomedical Research Ethics Committee, Govan Mbeki Building, University Road, Westville Campus, Tel: 031-260 2486/1074 Email: BREC@ukzn.ac.za

Note to Students:

PLEASE NOTE THAT ONLY ONE COPY OF APPLICATION AND SUPPORTING DOCUMENTS NEED BE SUBMITTED IF STUDY IS FOR DEGREE PURPOSES. ALL APPLICATIONS FOR DEGREE PURPOSES MUST BE SUBMITTED VIA THE COLLEGE POST-GRADUATE OFFICE WITH AN APPROVAL LETTER ATTACHED.

IF STUDY IS FOR NON-DEGREE PURPOSES THEN 3 COPIES MUST BE SUBMITTED TO BREC.

INCOMPLETE SUBMISSIONS MAY RESULT IN DELAYED REVIEW OF THE APPLICATION

For all expedited review applications:

- **3 TYPEWRITTEN COPIES** OF APPLICATION (Back-to-back (double-sided) copies preferred)
- **3 COPIES** OF THE PROTOCOL
- **3 COPIES** OF CURRENT CV/s **(**abbreviated max 4 PAGES)
- **3 COPIES** OF EVIDENCE OF CURRENT GCP / RESEARCH ETHICS TRAINING *requirements below
- **3 COPIES** OF ALL QUESTIONNAIRES TO BE USED IN THE STUDY
- **3 COPIES** OF THE INFORMED CONSENT FORMS (See BREC templates)
- **3 COPIES** OF THE PATIENT INFORMATION LEAFLET (See BREC templates)
- HAVE YOU FAMILIARISED YOURSELF WITH THE BREC TERMS OF REFERENCE? (See http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx)

- DETAILS OF ALL FUNDING SUPPORT?
- ALL PERSONAL INFORMATION?
- ANSWERED ALL QUESTIONS?
- GIVEN DETAILS OF ALL RESEARCH PRESENTLY BEING UNDERTAKEN?
- DELETED UNNECESSARY BLANK SPACES IN THE DOCUMENT?
- **IS DECLARATION PAGE SIGNED BY PI/SUPERVISOR AND ACADEMIC LEADER/H**

*** Requirement for this application is as follows:**

Online TRREE Module 1 (Introduction) and then the South Africa specific TRREE module certificates are required. There is no need to do TRREE modules 2-4 unless you choose to do them as relevant to your study design or sample, or for educational purposes. Current Good Clinical Practice (GCP) certification is required for clinical trials and interventional studies. BREC reserves the right to request a GCP certificate for interventional studies that are not formal clinical trials. The NIH online module may be compulsory for PIs who are funded by US Federal
Agencies (e.g. NIH, NIMH, DAIDS, etc) – this is a funder requirement. Ethics certificates expire after 3 years unless otherwise stated by the issuer of the certificate. **(Links on BREC website http://research.ukzn.ac.za/Research-Ethics/Biomedical-ResearchEthics.aspx)**

Appendix 3: The Guidelines for Authorship for the Journal selected for submission of the manuscript (below)

African Health Sciences Journal

INSTRUCTIONS TO AUTHORS.

SUBMITTING A MANUSCRIPT

The manuscript should be submitted online on Manuscript Central on the following website:

http://mc.manuscriptcentral.com/mums-ahs

Editorial enquiries should be sent by email to:

The Editor,

African Health Sciences,

Makerere University School of Medicine, College of Health Sciences

P. O. Box 7072, Kampala, Uganda.

Fax: +256-41-530022,

Email: kabaleimc@gmail.com

Tel +256-41-530020/1; +256 772 494120.

Authors may also contact the Editorial Office for status requests regarding their submissions: Benidictor Muhwezi (benidictmak@gmail.com).

We accept a manuscript on the understanding that it is reporting unpublished work and that it is not under consideration for publication elsewhere. We generally accept manuscripts in the following categories: reports of original research, case reports, special articles, letters to the editor and reviews.

PREPARATION OF MANUSCRIPTS

African Health Sciences fully endorses the Uniform Requirements for Manuscripts (URM) issued by the International Committee of Medical Journal Editors ICMJE, details of which can be accessed on: http://www.icmje.org

LENGTH OF MANUSCRIPTS

Full-length articles should not exceed 3000 words and have a maximum of six tables (or figures). Short reports should be less than 1500 words with a maximum of two tables (or figures). Letters to the Editor and Book reviews should be less than 1500 words and do not need an abstract.

FORMATTING

Manuscripts should be written in English and typed to fit on single-sided A4size pages, with margins of at least 25mm. Research articles should include the following, each beginning on a fresh page: title, abstract, introduction, methods, results, discussion, references, acknowledgements. All illustrations, figures, and tables should be placed within the text at the appropriate points, rather than at the end.

TITLE PAGE

This should contain an informative title, the first name, initial and last name of each author. The page should also include the name of institution(s) and departments to which the work should be attributed, and the name, address, email, fax, and telephone numbers (s) of the author responsible for correspondence about the manuscript. We also require the email addresses of ALL authors. **On acceptance, the list of authors will not change.**

ABSTRACT

The abstract must not exceed 250 words and must be structured as follows: Background, Objectives, Methods, Results, and Conclusions.

ACKNOWLEDGEMENT.

This should be on a separate page and not be more than ten printed lines (about 500 bytes).

FIGURES AND TABLES AND SCIENTIFIC MEASUREMENTS.

1. Figures and tables should be of reproducible quality, include comprehensive captions and not duplicate material presented in the text. All illustrations (tables and figures) must be cited consecutively in the text. Avoid internal vertical or horizontal lines in tables.
2. Any figures should be professionally designed and submitted as original copies. • All scientific measurements except blood pressure (mm Hg) should be expressed in SI units. REFERENCES: (Vancouver style).
3. The references must be in the following form: author (s), title of journal article, full name or Index Medicus or Medline or PUBMED abbreviation of journal, year of publication, volume number, and page numbers in full. When there are six or fewer

authors, list all of them. If there are seven or more, then list the first six followed by et al. Examples of references:

Journal reference:

Oyedeji GA. Delayed sexual maturation in sickle cell anaemia patients-observations in one practice. Annals of Tropical Paediatrics 1995; 15 (3): 197-201

Book reference:

Campbell JM, Machin D. Medical Statistics: a common sense approach. 2nd ed. New York: John Wiley & Sons, 1993 References to personal communication, unpublished material or manuscripts in preparation or submitted, but not yet accepted, are discouraged.

Permission to reproduce borrowed material: Written permission to reproduce borrowed material (Illustrations, tables and figures) must be obtained from the original publishers and authors, and submitted with the manuscript. Borrowed material should be acknowledged in captions Conflict of interest disclosure Authors: African Health Sciences requires all authors to disclose conflict of interest.

According to the ICMJE (http://www.icmje.org/ethical_4conflicts.html), this includes "all financial and personal relationships that might bias their work". The authors have to say "whether potential conflict does or does not exist." African Health Sciences expects authors to declare presence or absence conflict of interest in the manuscript. This must be written on a separate page, giving detail where applicable, of the conflict of interest if it exists.

CHECKLIST FOR AUTHORS

Before submitting your manuscript please make sure you have the following:

1. Covering (submission) letter
2. Corresponding author's name, complete address, institution, title, telephone number, fax number, and e-mail.
3. Complete address, degrees, institution, title, telephone number, and e-mail for each author
4. Manuscript in Microsoft Word, or RTF
5. Conflict of interest disclosure
6. Proposed list of potential reviewers

7. Submit your manuscripts on : http://mc.manuscriptcentral.com/mums-ahs

Appendix 4: Ethics approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

16 July 2021

Dr S Moodley (206501362)
School of Clinical Medicine
College of Health Sciences
sharmoodley@gmail.com

Dear Dr Moodley

Protocol: The association between headache presentation, clinical examination and radiological findings: A retrospective analysis of patients presenting to a tertiary referral centre
Degree: MMed
BREC Ref No: BE134/19

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	**18 July 2021**
Expiration of Ethical Approval:	**17 July 2022**

I wish to advise you that your application for recertification received on 09 July 2021 for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee (BREC).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 10 August 2021.

Yours sincerely

[redacted]

.....
Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Appendix 5: Department of Health approval letter

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2605/ 3188/ 3 26 Fax: 033 394 3760
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_201906_009

Dear Dr S. Moodley
UKZN

Approval of research

1. The research proposal titled '**The association between headache presentation, clinical examination and neuro-imaging findings: A retrospective analysis of patients presenting to a tertiary centre** ' 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. Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
   b. Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.
   c. Provide an interim progress report and final report (electronic and hard copies) when your research is complete 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 2905.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 03/07/19

Fighting Disease, Fighting Poverty, Giving Hope

z

Appendix 6: Permission to conduct research approval letter

APPENDIX 9

PERMISSION TO CONDUCT A RESEARCH STUDY/TRIAL

This must be completed and submitted to the Medical Superintendent/s / Hospital Manager for signature.

For King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH) studies please submit together with the following:

i) Two copies of the final, approved protocol
ii) Letter giving provisional ethical approval
iii) Details of other research presently being performed by yourself (individually or as a collaborator)
iv) Details of any financial or human resource implications to King Edward VIII Hospital
v) If a clinical trial, please produce proof of payment or intention thereof to KEH

Once the document has been signed it should be returned to this office so that full ethical approval can be granted.

To: Hospital Manager

PROTOCOL

Permission is requested to conduct the above research study at the hospital/s indicated below:

Site 1 address:

Inkosi Albert Luthuli Central Hospital
PDD Vuri Mzimela Road,
Cato Manor, 4091

Investigator/s:
Principal: Dr. Sharmila Maistry
Co-Investigator: _____
Co-Investigator: _____

Signature of Hospital Manager : [redacted]

Date: 29/05/2019

Site 2 address: Investigator/s

_____ Principal: _____
_____ Co-Investigator: _____
_____ Co-Investigator: _____

Signature of Hospital Manager :

_____ Date: _____

NB: Hospital Manager/s to send a copy of this document to Natalia.

Appendix 7: Approved research letter from Medical manager IALCH

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X03, Mayville, 4058
Tel: 031 240 1060 Fax: 031 240 1564 Email: [redacted]
www.kznhealth.gov.za

Office of The Medical Manager
IALCH

23 May 2019

Dr S Moodley (206501362)
School of Clinical Medicine
College of Health Sciences

Dear Dr Moodley

Re: Approved Research: Ref No: BE 134/19: The association between headache presentation, clinical examination and radiological findings: A retrospective analysis of patients presenting to a tertiary referral centre.

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] N Tasbuali

Dr L P Mtshali
Medical Manager / Acting

Appendix 8: Approved letter from Medical manager to conduct research

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE,

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: [illegible]@ialch.co.za
www.kznhealth.gov.za

Office of The Medical Manager
IALCH

Reference: RH 134/19
Enquiries: Medical Management

22 May 2019

Dr S Moodley (206501362)
School of Clinical Medicine
College of Health Sciences

Dear Dr Moodley

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **The association between headache presentation, clinical examination and radiological findings: A retrospective analysis of patients presenting to a tertiary referral centre.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted] Dr N Takuwa

....

Dr L P Mtshali
Medical Manager /Acting

Fighting Disease, Fighting Poverty, Giving Hope