# SENSITIVITY AND SPECIFICITY OF FUNDUSCOPY IN DETERMINING THE NEED FOR BRAIN COMPUTED TOMOGRAPHY IN PATIENTS PRESENTING WITH NEW-ONSET HEADACHE

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of Master of Medicine in the division of Neurology

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# i. DECLARATION

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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## ii. DEDICATION

To my mom and my loving husband for their unconditional love and support.

## iii. PUBLICATIONS AND PRESENTATIONS ORIGINATING FROM THIS RESEARCH

## iv. ETHICAL CONSIDERATIONS

Permission for this prospective study was obtained from Professor G. Modi (Head of Division of Neurology, Department of Neurosciences) and the Human Research Ethics Committee of the University of Witwatersrand (clearance number – M170714).

## v. ABSTRACT

***Introduction:*** Headache is a highly prevalent debilitating disorder. Computerized tomography of the brain (CTB) is commonly requested in patients with new-onset headache. This places a tremendous burden on the public health system. Our study aims to describe new-onset headache, its relationship to funduscopy and then relate the likelihood of finding an abnormality on CTB scan.

***Methods:*** This was a prospective study of adult patients presenting with new-onset headache. History of comorbidities was noted. A full neurological examination was done to ascertain if focal signs were present. Funduscopy was performed and radiological data collected. Fisher's exact test was used to assess significant associations between funduscopy, focal signs and CTB scan. A p-value of <0.05 was considered significant. Cohen's Kappa test was done to assess if the probability of agreement of fundoscopy and CT findings are by chance alone. A value of less than 0.40 was considered a fair agreement.

***Results:*** One-hundred and eight patients were included in this study. Forty-six (43%) had abnormal CTB scan findings. The most common abnormalities were focal brain lesions and cerebrovascular incidents. Twenty-five patients (23%) had abnormal funduscopy findings of which papilloedema and retinopathy were the most common. The sensitivity of fundoscopy in detecting abnormalities on CTB scans prior to stratification into "focal- and no focal signs" groups, was low (36%) but the specificity was high (87%). In patients with focal signs the sensitivity was still low (44%) but specificity was 100%. In the group with no focal signs the sensitivity was extremely low (16%), but the specificity was high (71%).

***Conclusions:*** In patients with new-onset headache, abnormalities on funduscopy with or without focal signs have high a specificity but a low sensitivity in predicting abnormalities on CTB scan and cannot be recommended as effective screening tools in our setting.

## vi. ACKNOWLEDGMENTS


- I want to thank my supervisor, Professor G Modi, for his support, guidance and knowledge.
- I would like to also express my gratitude to the consenting participants of the study.

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## x. NOMENCLATURE

| | |
|---|---|
| ACR | American College of Radiology |
| App | Application Software |
| CNS | Central nervous system |
| CTB | Computed Tomography of the Brain |
| CVA | Cerebral Vascular Accident |
| CVT | Cerebral Venous Thrombosis |
| DO | Direct Ophthalmoscopy |
| ENT | Ear Nose and Throat |
| HIV | Human Immunodeficiency Virus |
| ICH | Intracranial Haemorrhage |
| ICHD-3 | International Classification of Headache Disorders - version 3 |
| MRI | Magnetic Resonance Imaging |
| NPV | Negative Predictive Value |
| OPD | Out-patient department |
| PO | PanOptic |
| PPV | Positive Predictive Value |
| TTH | Tension-Type Headache |
| WHO | World Health Organization |

# 1 PROTOCOL AND EXTENDED REVIEW OF THE LITERATURE

## 1.1 Introduction

Headache is a common disabling condition.[1] The investigation of choice in patients presenting with new-onset headache is computerized tomography of the brain (CTB), but due to the high prevalence of headache disorders, this approach places a significant burden on the public health system in South Africa. [2-7] This study aims to describe headache and its relationship to funduscopy and CTB scan findings. Additionally, focal signs, comorbidities and headache characteristics are described in relation to abnormalities on CTB scan.

## 1.2 Headache Prevalence

Headache is a common disorder with a global prevalence of approximately 50% in adults.[1] Headache is considered the fourth most common complaint and the foremost neurological complaint of patients presenting to the emergency department.[9] There is significant morbidity associated with the condition as eloquently shown in the Global Disease Study where it was rated as the second leading cause for years lived with disability.[8] In Sub-Saharan Africa, the one-year prevalence ranges from 45% in Ethiopia to 62% in Zambia.[3, 4, 8]

To date, South African headache statistics regarding prevalence, especially new-onset headache, is scarce. An unpublished study conducted at the Durban University of Technology, found the prevalence of headache in students to be 58%.[5]

Headaches can present alone or in association with focal neurological deficits such as reduced power, sensation, tone, coordination, vision, speech or swallowing.[10]

## 1.3 Primary and Secondary Headache Disorders

Primary headache disorders are headaches associated with no underlying medical aetiology, a normal neurological examination (except for migraine) and normal CTB scan.[11] Secondary headaches disorders are diagnosed when a headache occurs in close temporal relation to the demonstration of an underlying pathology known to cause headache either on examination or by special investigations.[12, 13]

### *1.3.1 Primary Headache Disorder Diagnosis*

Primary headache disorders are clinically diagnosed by making use of the International Classification of Headache Disorders (ICHD). The new ICHD-3 that replaced the trial "ICHD-beta" version was published in 2018 and describes an orderly classification with clear diagnostic principles for each headache entity. In this updated version of the ICHD-3, novel scientific evidence played a significant role in the diagnostic criteria set out for each headache entity. A diagnosis is made after a careful account of headache characteristics (phenotype), and the number of episodes is noted in the setting of a normal clinical examination. If diagnostic criteria are met the headache is classified into primary headache categories and subcategories, for example, tension-type headache, migraine, trigeminal autonomic cephalgias and other primary headache disorders.[13, 14] It has been shown that even earlier versions of ICHD criteria have a high sensitivity and specificity in the diagnosis of primary headache disorders.[15]

Neuroradiological imaging is unequivocally indicated in cases where the diagnostic criteria are not confidently met or if atypical features, the so-called "red flags" (as discussed below) are present in patients previously diagnosed with primary headache disorders.[16]

### *1.3.2 Secondary Headache Disorders*

The diagnosis of a secondary headache requires a thorough history, examination and further diagnostic workup to rule out life-threatening underlying conditions.[11] There should be a temporal relation to the onset of headache and the underlying aetiology.[13]

Though prevalence and incidence of primary headache disorders are high in the global context, secondary headaches are common in Africa, ranging from infectious causes (for example tuberculosis, bacterial abscess, toxoplasmosis, cryptococcal meningitis, HIV-Human Immunodeficiency Virus) to uncontrolled hypertension.[8, 17]

Patients with abnormal neurological findings, including the ocular funduscopy, are more likely to have abnormal CTB scans.[18, 19]

### *1.3.3 Primary and Secondary Headache Correlated with Abnormalities on Funduscopy and CTB*

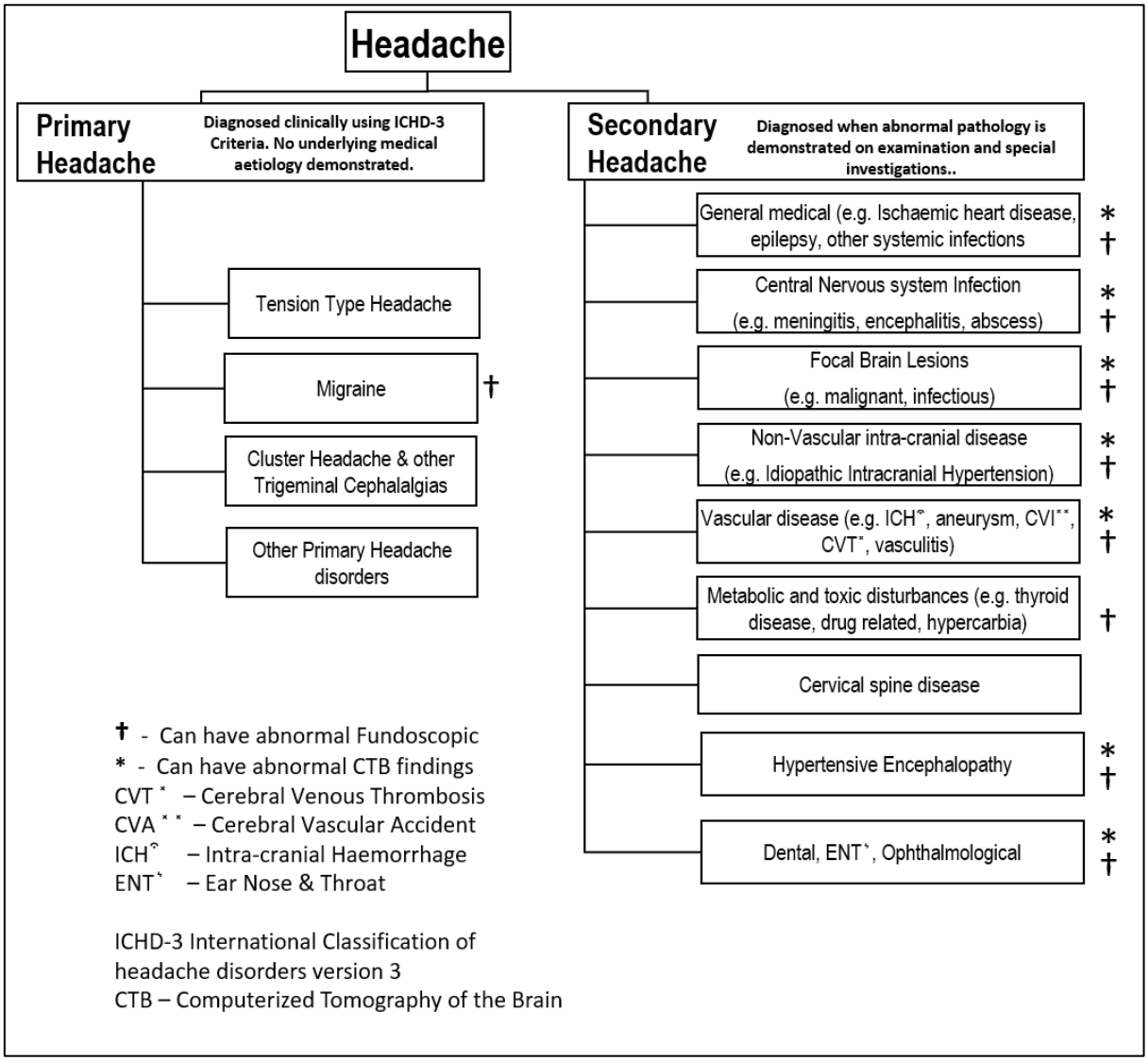


*Figure 1 – Types of headaches and their correlation to funduscopy and CTB* *13, 20-24*

Figure 1 broadly illustrates the two categories of headaches with examples. The possibility of finding abnormalities on CTB and Funduscopy is illustrated by using asterixis for the former and daggers for the latter.

#### *1.3.3.1 Primary Headache disorders associated with abnormal findings on funduscopy and CTB scan*

Retinal Migraines are considered migraine with an aura and present with reversible, monocular negative or positive visual phenomena.[13] Migraine patients reported visual-after-images following routine ocular funduscopy three times more commonly than control groups.[23] On Funduscopy in these patients, retinal arteries may be constricted, and the fovea may be more distinct with surrounding macular retinal pallor. The optic disc may be pale early and hyperaemic later in the aura.[24]

A complication of migraine. i.e. migrainous infarction is diagnosed when one or more aura symptoms occur in combination with an ischaemic brain lesion, in the appropriate region confirmed by neuro-imaging, with the onset during a typical aura attack. Some patients that complain of monocular visual disturbances have hemianopia. In a patient with new-onset retinal migraine, there should be a low threshold to request a CT scan of the brain to rule out a cerebrovascular incident.[25] Migrainous infarction typically occurs in younger females with a predilection for the posterior circulation. If an aura persists for more than 60 minutes, a migrainous infarction should be ruled out. It is also known that there is a twofold risk of ischaemic stroke in patients with migraine.[26]

#### *1.3.3.2 Secondary headaches associated with abnormal findings on funduscopy and CTB*

##### *1.3.3.2.1 Red flags as indicators of a possible underlying pathology*

Red flags for further investigation in patients with headache are well described, i.e., abnormal neurological examination; sudden-onset "worst headache"; new headache in patients over the age of 50 years; new-onset headache in immunocompromised patients; progressively worsening headache; headache with signs of meningitis (fever, meningism; rash); papilloedema; headache aggravated by Valsalva manoeuvres;

headache associated with incoordination and dizziness; headache with seizures or decreased level of consciousness. [11] [27-29]

In patients with headache and papilloedema (easily recognizable on funduscopy), a CTB scan is of importance to rule out sinister conditions such as obstructive hydrocephalus, mass lesions, idiopathic intracranial hypertension or cerebral venous thrombosis.[30] [31]

*1.3.3.2.2 Intracranial Haemorrhage*

Subarachnoid haemorrhage typically presents with a thunderclap headache and is associated with cerebral aneurysms and trauma. A CTB scan within 6 hours of the diagnosis has a sensitivity and specificity of 100%.[32] Fundoscopic anomalies include optic disc swelling, retinal, sub-hyaloid and vitreous haemorrhages. [33]

*1.3.3.2.3 Infective Causes*

Infective causes of headache such as meningitis, encephalitis and brain abscesses typically have additional features such as meningism, fever and constitutional symptoms. [11, 21] Papilloedema is not uncommon in opportunistic infections such as cryptococcal meningitis or due to obstructive hydrocephalus in tuberculous meningitis. [34-36] If focal signs and papilloedema are present a CTB is indicated before doing lumbar puncture.[31]

In an immunocompromised (e.g. HIV, malignancy) patient presenting with a new-onset headache, a secondary cause such as metastatic disease or Central Nervous System infection must be excluded. Funduscopy can help diagnose Herpes Simplex or Cytomegalovirus retinitis in immunocompromised patients with symptoms of meningitis.

*1.3.3.2.4* Idiopathic Intracranial Hypertension

Idiopathic Intracranial Hypertension presents with subacute onset of headache and features of raised intracranial pressure such as nausea and vomiting. These patients frequently have papilloedema and transient visual disturbances. Though Magnetic Resonance Imaging with a Venogram is the preferred imaging modality of choice, CTB scan is usually the first investigation in these patients to rule out alternative causes of raised intracranial pressure.[37]

*1.3.3.2.5 Systemic and cerebrovascular disease*

A recent study showed that up to half of patients with ocular fundus abnormalities were attributable to undiagnosed systemic hypertension (isolated retinal haemorrhages) and had grade III or IV hypertensive retinopathy.[30, 38] Patients with undiagnosed or uncontrolled hypertension may present with headache in up to 20% of cases.[17, 34, 38] In these patients; microvascular abnormalities are strongly associated with an increased risk for strokes.[30] If hypertensive retinopathy is associated with focal signs, a CTB Scan is indicated to rule out cerebral vascular incidents. It has also been reported that large posterior circulation strokes are more commonly associated with new-onset headache.[34]

It is thus essential to know the indications and limitations of CTB and Funduscopy.

## 1.4 The value of CTB in the identification of pathology

Computed Tomography of the Brain is a valuable special investigation in the identification of pathologies, as shown in Figure 2.

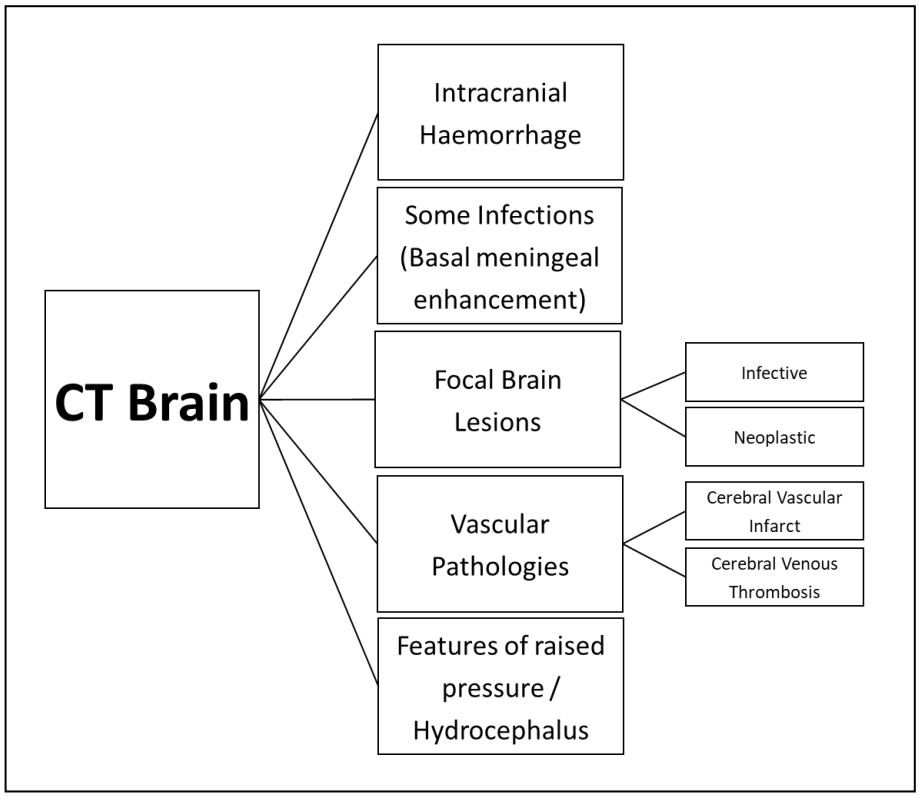


*Figure 2 – Possible pathologies that can be identified using CTB* [11, 22, 39]

### *1.4.1 CTB requests and appropriateness in headache patients*

Neuro-imaging is essential in the investigation of new-onset headaches. Though Magnetic resonance Imaging (MRI) is more sensitive in identifying pathology, a CTB scan is usually the first line of investigation in resource-limited settings. A CTB scan is typically requested in all new-onset headaches to rule out potentially treatable conditions. This notion is supported by the American College of Radiology (ACR) Appropriateness Criteria as an indication for requesting a CTB in new-onset headaches. The following rating scale is used in beforementioned criteria: 1, 2, 3 'usually not appropriate'; 4, 5, 6 'may be appropriate', and 7, 8, 9 'usually appropriate'. Depending on associated symptoms in new-onset headaches, the ACR score is usually, high indicating the appropriateness to request a scan.[22]

However, this practice places a significant burden on the resource-limited public sector of South Africa and Africa, where Computerised Tomography is limited to 1.2 units per

million, in the general population. This number is particularly shocking when compared to 40 units per million in the USA.[40]

## 1.5 The role of Funduscopy in headache

### *1.5.1 Funduscopy as non-invasive indicator of pathology*

Examination of the fundus is a fundamental part of the neurological examination in patients presenting with headache. Funduscopy is the only non-invasive opportunity to observe neurological tissue and microvasculature directly.[30]

Abnormalities can offer insight into both systemic and neurological disease aetiologies not picked up by physical examination alone.[41, 42] A normal neurological and funduscopic examination is associated with a less threatening cause of headaches. Funduscopy is an easy skill to learn and is an invaluable tool in screening patients with headache.[11]

### *1.5.2 Funduscopy Options*

There are various tools currently available to assess the optic nerve. The traditional direct ophthalmoscope has a 5° field of view in non-dilated pupils.

The Welch Allyn Panoptic ® Ophthalmoscope (PO) is now widely available. It has a larger 25° field of view, thus five times larger view of the fundus. It is mobile and affordable. An adapter, the Welch Allyn iExaminer attaches to the PO and allows the examiner to capture images of the fundus. A home-made adapter that functions similar to the iExaminer can be made for Android Phones.

*Figure 3 - Author's colleagues posing with the homemade device switched on.*

*Figure 4 – Mobile phone with an adapter to Panoptic® Ophthalmoscope*

In Figure 4 on the left a Samsung phone with a home-made adapter to Panoptic® Ophthalmoscope. In the same figure photo on the right the home-made adapter is shown (a PVC pipe was heated up with a hairdryer and attached to a phone case to make the adapter)

It has been demonstrated that a PO is more sensitive and specific than DO. Non-mydriatic ocular fundus photography with 45° field of view has gained popularity in the literature as the choice of imaging in clinical trials. The latter is, however, an expensive device and not as mobile as the PO.[41]

## 1.6 The need for further clinical studies

### *1.6.1 Indications for CTB scan in limited-resource environments*

Bezuidenhout et al. proposed a protocol for requesting urgent CTB scans in the resource-limited Northern Cape Province in South Africa, "The Kimberly Hospital Rule".[7] This protocol, though including sudden onset headache and focal signs, does not include abnormal funduscopy as a formal additional finding to motivate for an urgent CTB scan. This is not ideal, seeing that papilloedema is considered an essential red flag in a new-onset headache patient for further investigation.[31]

### *1.6.2 Practical use of Funduscopy in new-onset headaches*

A recent study by Bruce et al. assessed the sensitivity of direct Funduscopy compared to non-mydriatic ocular fundus photography done by emergency department (ED) physicians. The study found that direct Funduscopy was poorly and infrequently performed in the patient group (only 14% of patients had a funduscopic examination and none of the relevant pathological findings identified). Patients included presented with headache, focal neurological deficits, diastolic blood pressure >120mmHg and acute visual changes.[30]

This study was limited by comparing direct ophthalmoscopy (DO) with a 5° field of view in non-dilated pupils with 45°field non-mydriatic ocular fundus photography. A more useful comparison might have been made in using a Welch Allyn Panoptic ® Ophthalmoscope (PO) with a larger 25° field of view. It has been demonstrated that a PO is more sensitive and specific than DO.[41] The results of the study reported that 8.5% of the patients had abnormal funduscopic findings. This might be more than expected in the general population as the study was conducted in a specialized tertiary ED where it is probable that patients will have more severe pathological features than in a general clinic scenario. [43]

Though non-mydriatic ocular fundus photography is more sensitive than DO, DO is more readily available, mobile and less expensive. When connected to a smartphone, images can be sent to specialists easily for review and comment. The only application (app) used is the smartphone camera, and no software training or license or maintenance fees is required when using a cell phone. [44, 45]

## 1.7 Conclusion and reason for the study

It is clear from the literature review that there is an association between abnormal funduscopic findings and intracranial pathology identified by CTB in patients presenting with headache. This study aims to ascertain if an abnormal funduscopic examination and abnormal neurological examination can be used as a screening test to decrease the number CTB scans requested for headache patients in the resource-limited public sector.

## 1.8 Study Objectives

### *1.8.1 Primary Objective*

To assess the sensitivity of Funduscopy and correlating it with CTB findings in patients with new-onset headaches.

## 1.9 Methodology

### *1.9.1 Study Design*

A prospective cross-sectional study will be conducted over six months assessing neurological and funduscopic findings in patients presenting with new-onset headache and correlated with CTB scan results.

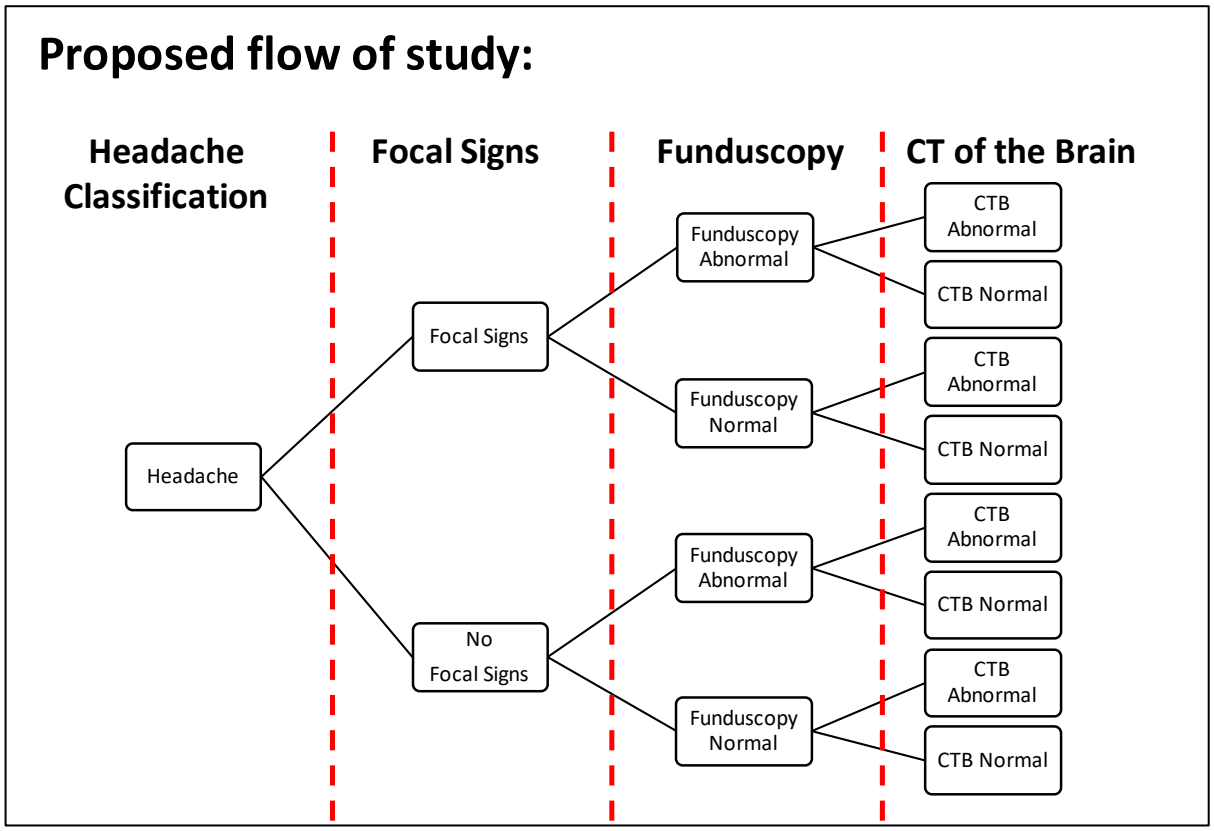


*Figure 5 – The proposed logic tree for the flow of the study.*

## 1.10 Statistical analysis

### *1.10.1 Study Setting*

- The study will be conducted at Charlotte Maxeke Johannesburg Academic Hospital.

### *1.10.2 Study Population*

All adults meeting eligibility criteria (see below), presenting with new-onset headaches to Charlotte Maxeke Johannesburg Academic Hospital within the six months of study recruitment will be asked to volunteer to take part in the study.

### *1.10.3 Eligibility Criteria:*

#### *1.10.3.1 Inclusion Criteria*

- All patients with new-onset headaches

*1.10.3.2 Exclusion Criteria*

- Renal dysfunction
- Iodine allergy
- Patients that are known with intracranial pathology (diagnosis made on previous neuroradiological investigation)

### *1.10.4 Sampling Methods*

Purposive non-probability sampling

### *1.10.5 Sample Size Calculation*

- Statistical software used for sample size calculation: Statcal/ Epi Info 7.1
- Number of headache patients seen over six months estimated at 240
- Precision 0.05
- Estimated frequency of presentation with new-onset headache 30%
- Acceptable margin of error 5%, 95% confidence interval
- No clusters and design effect =1
- Sample size (minimum)

Sample size (n) based on sensitivity = $\frac{Z^2_{a/2} \times S_N \times (1- S_N)}{L^2 \times Prevalence}$ of [46]

$Z^2_{1-a/2}$ = 1.96 (power of 80%)

$S_N$ – Anticipated sensitivity 95%

$L^2$ – Precision 0.05

Prevalence of headache estimated: 72% [4]

$$= \frac{1.96^2 \times 0.95\ (1-0.95)}{0.05^2 \times 0.72}$$

$$= 102$$

\+ *Assuming an attrition rate of 10%*

Minimum sample calculated: **112 patients**

### *1.10.6 Sample selection*

All consenting patients presenting with a new-onset headache that meet eligibility criteria from 1 September 2017- 28 February 2018 will be recruited.

### *1.10.7 Measurement Instrument/Tools*

A data sheet (included in Appendix A) will be completed for each patient consisting of:

- Demographic information: age, sex
- Headache related information: specific characteristics, duration and severity
- Associated features will be noted: nausea and vomiting, photophobia, fever
- CT Brain: findings normal or abnormal
- Funduscopy: normal or abnormal
- Any other co-morbidities will be noted.

### *1.10.8 Investigations*

All investigations performed are routine in any patient presenting with new-onset headache.

#### *1.10.8.1 CT scans*

- A radiologist will review all CTB scans.
- CT findings will be stratified into normal and abnormal findings, and significant associations will be tested using Chi-Square and Fisher's exact test
- Abnormal findings will be classified as focal brain lesions, white matter changes, meningeal anomalies, features of raised intracranial pressure, cerebral atrophy and additional findings
- A p-value $< 0.05$ will be considered significant. A statistician will be consulted regarding performing the formal data analysis

### *1.10.9 Funduscopy*

Funduscopy will be conducted with a Welch Allyn Panoptic® Ophthalmoscope.

- Findings will be stratified in normal/abnormal findings.
- A retinal photograph will be taken using the Panoptic® with a smartphone attachment for record purposes (Samsung S7 – Pro shooting settings, macro focus, 1.2x digital zoom, auto light, auto ISO, auto colour, standard lighting, maximum resolution)
- All funduscopic investigations will be done by the same registrar to reduce interobserver bias.

### *1.10.10 Data Analysis*

Data obtained in the datasheet (Appendix i: Data collection sheet) will be captured using an Excel spreadsheet.

This will be achieved using descriptive clinical analysis.

## 1.11 Ethics

- The protocol will be submitted for ethics approval to the Human Research Ethical Committee of the University of Witwatersrand.
- Consent, including consent for a contrast CTB scan, will be obtained from all study participants.
- Data confidentiality will be maintained by assigning participants study numbers. Neither patient names nor hospital numbers will be recorded on the datasheet. Any association between the study numbers, patient initials and identity, will be kept separate.

## 1.12 Study Limitations

- This study will be conducted at a single tertiary referral hospital. Patients referred for specialist assessment will likely have more severe symptoms than patients presenting with headache in the general population.
- This is small study and cannot be used to change current practice.

## 1.13 Funding

- Self. All investigations done are considered current practice in patients presenting with new-onset headache. No extra costs will be imposed on the patient or the hospital.

## 1.14 Timing

- The study will commence as soon as ethics approval is received. Patients will be recruited and enrolled in the study over a 6-month period. Data collection will occur simultaneously. Thereafter, data analysis and manuscript write-up will commence.

The Gantt chart in Table 1 shows the proposed timeline for the study.

*Table 1 – GANT chart showing the timeline of the study*

| | June- Sept 2017 | Oct 2017 | Nov 2017 | Dec 2017 | Jan 2018 | Feb 2018 | Mar 2018 | April 2018 | May 2018 | June 2018 | July 2018 | August 2018 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Literature review | | | | | | | | | | | | |
| Protocol preparation | | | | | | | | | | | | |
| Protocol Assessment | | | | | | | | | | | | |
| Ethics application | | | | | | | | | | | | |
| Data Collection | | | | | | | | | | | | |
| Data Analysis | | | | | | | | | | | | |
| Manuscript | | | | | | | | | | | | |

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# 2 MANUSCRIPT:

## SENSITIVITY AND SPECIFICITY OF FUNDUSCOPY IN DETERMINING THE NEED FOR BRAIN COMPUTED TOMOGRAPHY IN PATIENTS PRESENTING WITH NEW ONSET HEADACHE

## 2.1 Background

Headache is a common debilitating condition with a high global prevalence.[1-6] Neuro-imaging with computerized tomography of the brain (CTB) is the most used investigation to rule out an underlying sinister cause for the headache.[7] However, this places a significant burden on the public health system in South Africa, where Computerized Tomography (CT) is limited to a mere 1.2 units per million in the general population. The disparity in allocation is evident when one considers the allocation of 40 units per million population in the United States of America (USA).[8, 9]

Our study aims to determine the validity of funduscopy as a screening tool in determining the need for a CTB in patients with new-onset headache, with or without focal signs. Additionally, we describe the correlation between primary and secondary headaches to funduscopy and CTB scan findings.

Headache is classified as either primary or secondary. Primary headache disorders are not associated with an underlying medical condition, typically have no focal neurological signs (with the exception of migraine) and have a normal CTB scan.[10] Primary headaches are clinically diagnosed by using the highly sensitive and specific International Classification of Headache Disorders (ICHD-3).[11-13] Imaging and other investigations are non-contributory in making the diagnosis of primary headaches.[14]

Secondary headaches disorders are diagnosed when a headache occurs in close temporal relation to an underlying pathology known to cause headache either on examination or by special investigations.[11, 14]

The diagnosis of a secondary headache requires a thorough history, examination and further diagnostic workup to rule out life-threatening conditions.[10, 14] Though prevalence and incidence of primary headache are globally high, secondary headaches are common in Africa due to the higher burden of non-communicable

disease.[15,16,17] The aetiology of these secondary headache ranges from infectious causes to headaches due to uncontrolled hypertension.[6, 18] Patients with abnormal neurological findings are more likely to have secondary headache disorders and abnormal CTB scans.[19]

“Red flag” screening tests have been developed to alert physicians to possible life-threatening causes of headache. Red flags include: Systemic signs such as fever; focal neurological symptoms and signs; onset of headache in a patient over the age of 50 years of age; abrupt onset of headache; papilloedema and positional or Valsalva induced provocation of headache.[7, 20]

Examination of the fundus is a fundamental part of the neurological examination in headache. Funduscopy is the only non-invasive opportunity to directly observe neurological tissue and microvasculature in order to diagnose disease aetiologies not detected by physical examination alone.[21-23] The traditional direct ophthalmoscope offers a 5° field of vision, while the now widely available Welch Allyn Panoptic ® Ophthalmoscope offers a 25° field of view.[22] A normal neurological, and funduscopic examination is usually associated with a less threatening cause of headache. If funduscopy is abnormal, a CTB scan is of importance to rule out an underlying pathological cause. [7, 10, 21]

CTB scan is a valuable special investigation in the diagnosis of pathological processes such as intracranial haemorrhage, infection, focal brain lesions, vascular pathologies and raised intracranial pressure.[10 24, 25]

## 2.2 Methods

### *2.2.1 Design and setting*

This prospective study was a primary data collection, conducted by the first author (ECS), and patients were recruited from the Charlotte Maxeke Johannesburg Academic Hospital, a tertiary level public hospital in South Africa's Gauteng province, from January 2018 to June 2018.

One-hundred-and-fourteen consenting adult patients presenting with new-onset headache admitted to the medical wards and seen at the neurology outpatient department (NOPD) were enrolled in the study. Patients that were unable to receive contrast for the CTB scan due to renal dysfunction (self-reported or by laboratory results) and patients with known intracranial pathology (diagnosed on previous imaging) were excluded. Those who appeared unwilling, unable to give informed consent or incapable of coming for the CTB scan were excluded. The study was approved by The University of Witwatersrand Human Research Ethics Committee (clearance number M170714 – see Appendix iii).

One-hundred-and-eight participants completed the study. Six participants were excluded due to being unable to come in for the required CTB scan. Reasons for defaulting the appointment included relocation and transport problems.

### *2.2.2 Measures*

A structured interview was administered, and neurological examination was carried out on all participants.

Focal neurological signs were noted as present if any deficits such as abnormal power, sensation, tone, coordination, vision, speech or swallowing were present.

Funduscopy was performed using a Welch Allyn Panoptic® Ophthalmoscope. Findings were stratified as normal or abnormal (papilloedema, retinopathy, optic disc pallor, haemorrhages). A retinal photograph was taken using the Panoptic® with a smartphone attachment for record purposes. All funduscopic investigations were done by the same registrar to reduce interobserver bias.

As per department protocol, CTB scans were ordered for all participants with new-onset headaches. The scans were reviewed and reported by a radiologist. CT findings were stratified into normal and abnormal findings. Abnormal findings were classified into focal brain lesions, white matter changes, meningeal anomalies, features of raised intracranial pressure, cerebral atrophy and additional/other findings.

A data sheet was completed for each participant capturing demographic information and headache-related information, e.g. specific characteristics in order to be classified as primary or secondary headache based on the ICHD-3 classification. (Appendix ii)

### 2.3 Statistical analysis

Patient demographics, clinical and headache characteristics were described quantitatively using frequencies and percentages. The sensitivity, specificity, positive predictive value (PPV), as well as negative predictive value (NPV), were calculated using funduscopy findings and comparing it to CTB scan findings (normal vs abnormal). A p-value of $<0.05$ was considered significant. Cohen's Kappa test was done to assess if the probability of agreement of fundoscopic and CT findings are by chance alone, a value of less than 0.40 was considered a fair agreement.[23] Statistical analysis was performed using Statistica Version 13.

## 2.4 Results

### *2.4.1 Demographics and data summary*

During the period 17 January 2018 to 29 June 2018, 114 patients with new-onset headaches were enrolled in this study; six were subsequently excluded as they did not follow up for the CTB scan. Of the remaining 108 patients, their median age was 39 years; 63% were female, and 79% were black Africans, as shown in Table 2.

*Table 2 - Sample (n=108) Demographic characteristics of study population.*

| Variable | Characteristics | Frequency | Percentage |
|---|---|---|---|
| **Race** | Black | 85 | 79% |
| | White | 16 | 15% |
| | Asian | 4 | 4% |
| | Coloured | 3 | 3% |
| **Gender** | Female | 68 | 63% |
| | Male | 40 | 37% |
| **Age** | 18-29 | 35 | 32% |
| | 30-39 | 34 | 31% |
| | 40-49 | 15 | 14% |
| | >50 | 24 | 22% |

Based on the ICHD-3 classification, 49 patients (45%) were diagnosed with primary headache disorders. Four per cent of patients could not be diagnosed confidently as primary headaches disorders, as they did not meet the number of events required to meet ICHD-3 criteria. They were classified as probable primary headache disorders. Just over half of the study sample (51%) was diagnosed with secondary headache disorders.

The greater majority of patients (80%) had no focal signs on clinical examination, as shown in Table 3.

The most common abnormalities noted on CTB scan findings were focal brain lesions and cerebrovascular incidents. The most frequent abnormalities on funduscopy were papilloedema and retinopathy.

*Table 3 – Sample (n=108) Clinical characteristics of headaches, funduscopy and CTB findings*

| Variable | Characteristics | Frequency (n) | Percentage |
|---|---|---|---|
| **Headache** | | | |
| Primary headache | Yes * | 49 | 45% |
| Probable primary headache disorder | Yes ** | 4 | 4% |
| Secondary headache disorders - | Yes *** | 55 | 51% |
| **Focal Signs** | | | |
| | Yes | 22 | 20% |
| | No | 86 | 80% |
| **Comorbidities** | **Yes** | **65** | **60%** |
| **CT Findings** | **Abnormal** | **46** | **43%** |
| | *Focal brain lesions* | *21* | *19%* |
| | *Cerebrovascular Incident* | *14* | *13%* |
| | *Other* | *8* | *7%* |
| | *Hydrocephalus* | *3* | *3%* |
| | *White matter changes* | *1* | *1%* |
| | *Cerebral atrophy* | *1* | *1%* |
| | *Intracranial Haemorrhage* | *1* | *1%* |
| **Funduscopy finding** | **Abnormal** | **25** | **23%** |
| | *Papilloedema* | 12 | 11% |
| | *Retinopathy* | 7 | 6% |
| | *Optic disc pallor* | 6 | 6% |
| | *Intraocular haemorrhages* | 1 | 1% |

* *- Based on ICHD-3*
** *- Did not meet ICHD-3 criteria to fulfil type or subtype of primary headache disorder, not fulfilling criteria for another headache disorder, no obvious causal aetiology found to diagnose as a secondary headache disorder*
*** *- A causal relationship to known secondary aetiology*

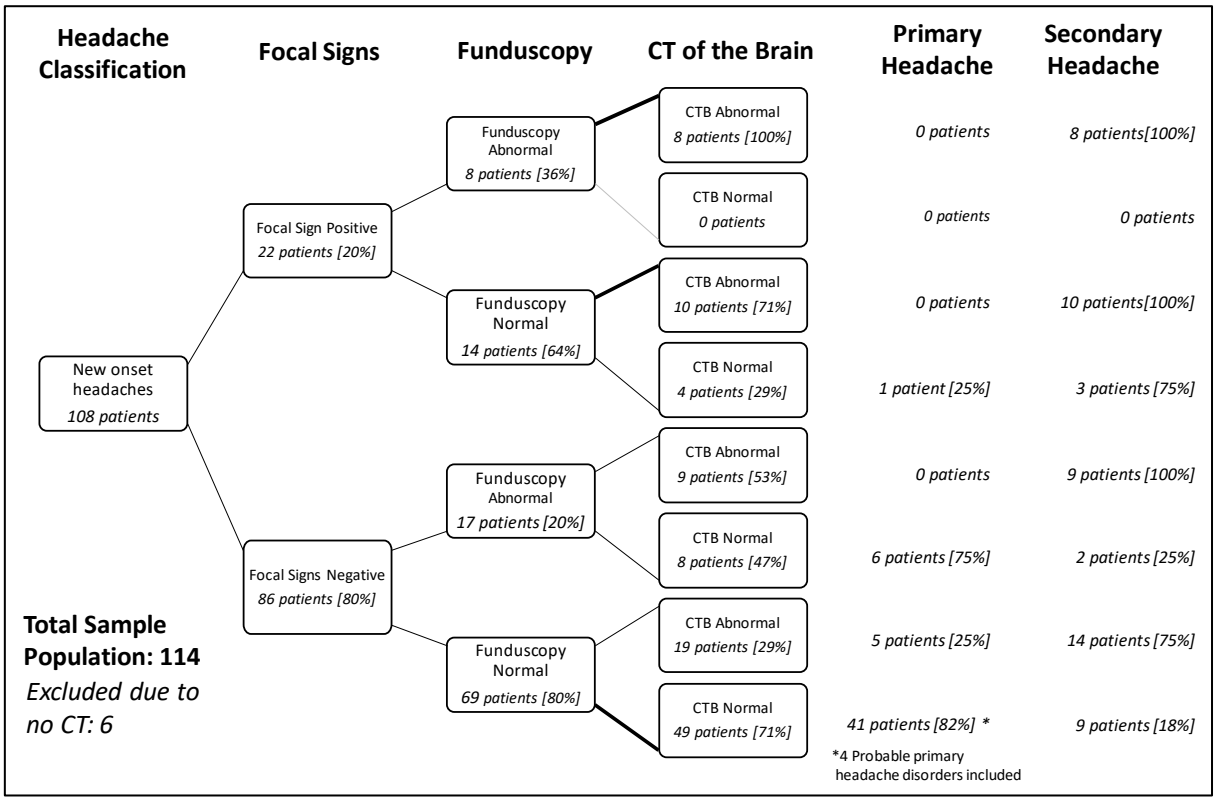


*Figure 6 – Study results summary*

Twenty-two patients had focal signs on examination. Eight patients with focal signs had abnormal funduscopy and an abnormal CTB scan and were subsequently diagnosed with secondary headache disorders. The remaining fourteen patients in the group with focal signs had normal funduscopy, of whom10 had abnormal CTB findings, as shown in Figure 6.

The majority of patients with no focal signs had normal funduscopic findings (80%) and subsequently had a normal CTB scan (71%). There was also a high number of primary headache disorders (82%) as defined by the ICHD-3 in this group.

### *2.4.2 Sensitivity and specificity of funduscopy in patients with new-onset headache*

High specificity but low sensitivity was noted when fundoscopy was correlated to CTB findings in relation to funduscopy in the study population as a whole, as shown in Table 4.

*Table 4 – Sensitivity and specificity of funduscopy in patients with new-onset headache*

| Number of Patients: 108 | | CT Findings | | | p-value |
|---|---|---|---|---|---|
| | | Abnormal | Normal | Total | |
| Funduscopy findings | Abnormal | 17 | 8 | 25 | 0.0037 |
| | Normal | 30 | 53 | 83 | |
| | Total | **47** | **61** | **108** | |

*Sensitivity 36%; Specificity 87% Cohen's Kappa 0.236*

When assessing patients with focal signs, fundoscopy had a specificity of 100% but a low sensitivity, as shown in Table 5.

*Table 5 - Sensitivity and specificity of funduscopy in patients with a new-onset headache with focal signs*

| Number of Patients: 22 | | CT Findings | | | p-value |
|---|---|---|---|---|---|
| | | Abnormal | Normal | Total | |
| Funduscopy findings | Abnormal | 8 | 0 | 8 | 0.1368 |
| | Normal | 10 | 4 | 14 | |
| | Total | **18** | **4** | **22** | |

*Sensitivity 44%; Specificity 100%; Cohen's Kappa 0.2254*

When assessing patients without focal signs, the sensitivity was extremely low (16%), but the specificity was high (71%), as shown in Table 6.

*Table 6 - Sensitivity and specificity of funduscopy in patients with new-onset headache without focal signs*

| Number of Patients: 86 | | CT Findings | | | p-value |
|---|---|---|---|---|---|
| | | Normal | Abnormal | Total | |
| Funduscopy findings | Abnormal | 8 | 9 | 17 | 0.0832 |
| | Normal | 20 | 49 | 69 | |
| | Total | **28** | **56** | **86** | |

*Sensitivity 16%; Specificity 71%; Cohen's Kappa; 0.1892*

## 2.5 Discussion

Our study aimed to determine the validity of funduscopy as a screening tool in determining the need for a CTB in patients with new-onset headache, with or without focal signs.

We found that fundoscopy has a low sensitivity but high specificity to predict abnormalities on a CTB scan in individuals with new-onset headaches.

### *2.5.1 New-onset headache findings prior to stratification into categories of focal and non-focal findings*

When assessing the study group, prior to stratification into a focal and a non-focal group, we found funduscopy to have a low sensitivity (36%) and high specificity (87%) to CTB scan findings. From this, we can deduct that funduscopy is not an ideal screening test to rule out or predict abnormalities (true positive rate) on the CTB scan. It is, however, a good test to identify patients that will likely have normal (true negative rate patients without the disease) CTB scans.[26, 27]

There are no studies to the author's knowledge that as a primary objective assessed the sensitivity and specificity of ocular fundus examination with correlation to CTB scan findings in patients presenting with new-onset headache.

Before the stratification, we found 68% (17 out of 25 patients) of our patients with an abnormal funduscopic examination had abnormalities on their CTB scans. This is similar to a finding by Thulasi et al., who reported that 76% (32 out of 42 patients) of patients that presented with a headache to the emergency department had abnormalities on funduscopy and an abnormal CTB scan.[28] The higher prevalence in their group can be attributed to the use of non-mydriatic ocular fundus photography which is much more accurate in identifying pathological features of the ocular fundus.[28]

All of their patients were seen in the emergency department, thus likely had more severe pathology. Sensitivity and specificity were not calculated in their study.[28]

### *2.5.2 New-onset headache findings in patients with focal signs*

When assessing new-onset headache patients with focal signs, funduscopy had a high specificity (100%) but a low sensitivity (44%). In our study normal funduscopy in patients with new-onset headaches and focal signs, could correctly identify almost all patients that would have normal CTB scans. All the patients in our study that had focal signs and abnormalities on funduscopy also had abnormalities noted on the CTB scan.

In the set of patients with new-onset headache, focal signs but normal fundoscopy (64%), a significant number had an abnormal CTB scan (71%) This illustrates that regardless of fundoscopy findings, patients with new-onset headache and focal signs need urgent CTB scans.

Our results are similar to studies by Stevenson et al.[17] and Locker et al.[29] who assessed the utility of an abnormal neurological examination (including funduscopy as part of this examination) as one of several factors in determining the likelihood of finding serious intracranial pathology on subsequent imaging. Neither study considered fundoscopy as an independent predictor of possible abnormalities. Like our study they found focal signs to be a significant predictor of intracranial pathology.[17, 29]

### *2.5.3 New-onset headache findings in patients without focal signs*

When assessing patients without focal signs funduscopy was not helpful to identify possible intracranial pathology.

A review by Evans combined numerous studies and assessed 3026 patients with new-onset headache and no neurological abnormalities. The study found neuro-imaging was normal in 98.1% of patients. In his review, fundoscopy was not noted as part of

the neurological examination at all. The discrepancy between their and our results might be due to the higher burden of non-communicable disease in our setting.[15, 30]

### *2.5.4 Findings in new-onset primary headache disorders*

Forty-five per cent of patients in this study were diagnosed with primary headache disorders.

In our study, patients diagnosed with a primary headache disorder based on the ICHD-3 were likely to have a normal funduscopic examination and normal CTB scan.[11] This finding is in keeping with published results of Eriksen et al. who demonstrated diagnostic accuracy even using older versions of the International Classification of Headache Disorders.[32] A recent study by Dong et al. showed the updated ICHD-3 version to be even more sensitive. Neuro-imaging was found to be generally normal and non-contributary to the diagnosis of primary headache disorders.[13]

### *2.5.5 Findings in new-onset secondary headache disorders*

In our cohort, 51% of patients were classified as having a secondary headache disorder. This is a very high number compared to international epidemiological studies where the incidence of life-threatening secondary headaches are estimated to be 3-5% and primary headache disorders are more prevalent.[28,32]

CTB scan abnormalities in patients with secondary headache disorders were predominantly cerebrovascular incidents and infective focal brain lesions. The high incidence is in accordance with the high incidence of these comorbidities in our setting.[27]

In our patients with focal signs and secondary headache disorder, all had abnormal funduscopy and abnormal CTB scan findings. Papilloedema was noted with a high frequency in our study, associated mainly with focal brain lesions and meningitis.

This important finding was also highlighted in a recently published paper by Do et al. that assessed the value of "red flags" in patients with secondary headache disorders. Although their review was based on data gathered from developed countries where secondary headache disorders are infrequent their findings are similar to ours. Their study found "abnormal neurological findings" as well as papilloedema are definite “red flags” and therefore indications to request a CTB scan urgently in patients presenting with secondary headaches.[20, 31]

In patients with secondary headache disorder without focal signs, the majority (23 out of 34) of patients had abnormal CTB findings. Only 11 of the 34 patients with secondary headache disorders had abnormal funduscopy. Funduscopy is thus also not an eloquent test to use in prediction of secondary headache disorders or pathology on CTB scan.

Clinicians and policymakers need to acknowledge the significant limitations of funduscopy as a screening test when requesting CTB scans in patients with new-onset headache.

### 2.6 Limitations

The study had several limitations. The recruited patients were restricted to a single tertiary hospital in South Africa; thus, only patients with headache severe enough to be referred to a tertiary facility were included.

Although the sample was sufficient based on the initial calculation of the sample size, it is still a small sample size and should not alter current practice before further studies corroborate the findings noted in this study.

The funduscopic findings were all done and interpreted by a single neurology registrar; thus, though interobserver bias was avoided, it would have been ideal if findings were confirmed by a second investigator.

## 2.7 Conclusion

- New-onset headache is a common presenting complaint in tertiary care facilities.
- In patients with new-onset headache, funduscopy has a low sensitivity and is not an ideal screening test to rule out or predict abnormalities on the CTB. The high specificity, however, makes it an excellent test to identify patients that will likely have normal CTB scans.
- The majority of patients diagnosed with primary headache disorder based ICHD-3 had normal CTB scans irrespective of funduscopy findings.
- Patients with secondary headache disorders are more likely to have an abnormal CTB scan. In our context, more than half of the patients were diagnosed with secondary headache disorders requiring a CTB scan.
- Funds for state sector radiological services should be a priority.
- More extensive studies are required to substantiate the findings of this study.

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# 3 APPENDICES

## APPENDIX I: DATA COLLECTION SHEET

| **Demographic Data** | | | |
|---|---|---|---|
| Study Number | | | |
| Date | | | |
| Age | | | |
| Sex | Male | | Female |
| **Headache History** | | | |
| Date of Onset | | | |
| Headache history suggestive of primary headache syndrome | Migraine without aura | Migraine with aura | Tension-Type Headache |
| | Cluster Headache | Paroxysmal Hemicrania | Short-lasting unilateral neuralgiform headache attacks |
| | Hemicrania Continua | Primary cough headache | Primary exercise headache |
| Diagnosis made clinically by ICHD3 Diagnostic Criteria - | Primary headache associated with sexual activity | Cold Stimulus Headache | Primary Stabbing Headache |
| | Nummular Headache | Hypnic Headache | New daily persistent headache (NDPH) |
| Focal signs | Yes | | No |
| Associated symptoms | Fever | | Nausea/Vomiting |
| | Meningism | | Photo/phonophobia |
| | Other: | | |
| Severity Verbal Rating Scale (VRS-6) | 1. No Pain | 2. Mild Pain | 3. Moderate Pain |
| | 4. Severe Pain | 5. Very Severe Pain | 6. Most severe pain imaginable |

| | | |
|---|---|---|
| Co-morbidities | | |
| Diabetes | Yes | No |
| Hypertension | Yes | No |
| Epilepsy | Yes | No |
| Asthma | Yes | No |
| TB | Yes | No |
| HIV | Yes | No |
| Other: | | |
| CT Findings (Radiologist Review) | | |
| Normal | Abnormal | |
| | Focal brain lesions | |
| | White matter changes | |
| | Cerebral atrophy | |
| | Cerebrovascular Incident | |
| | Intracranial Haemorrhage | |
| | Hydrocephalus | |
| Additional Findings: | | |
| Fundoscopic Findings Neurology Registrar | | |
| Normal | Abnormal | |
| | Papilloedema | |
| | Optic Disc Pallor | |
| | Intra-ocular haemorrhages | |
| | Retinopathy | |
| Other | | |

## APPENDIX II: ICHD3 DIAGNOSTIC CRITERIA – MAJOR PRIMARY HEADACHE DISORDERS

| | YES | NO |
|---|---|---|
| **Migraine without aura** | | |
| A. At least five attacks1 fulfilling criteria B–D | | |
| B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) | | |
| C. Headache has at least two of the following four characteristics: | | |
| *1. unilateral location* | | |
| *2. pulsating quality* | | |
| *3. moderate or severe pain intensity* | | |
| *4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)* | | |
| D. During headache at least one of the following: | | |
| 1. Nausea and/or vomiting | | |
| 2. Photophobia and phonophobia | | |
| E. Not better accounted for by another ICHD-3 diagnosis. | | |
| **Migraine with aura:** | | |
| A. At least two attacks fulfilling criteria B and C | | |
| B. One or more of the following fully reversible aura symptoms: | | |
| 1. visual | | |
| 2. sensory | | |
| 3. speech and/or language | | |
| 4. motor | | |
| 5. brainstem | | |
| 6. retinal | | |
| C. At least two of the following four characteristics: | | |
| 1. At least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession | | |
| 2. Each individual aura symptom lasts 5-60 minutes | | |
| 3. At least one aura symptom is unilateral | | |
| 4. The aura is accompanied, or followed within 60 minutes, by headache | | |
| D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded | | |

| **Tension-Type Headache:** | | |
|---|---|---|
| A. At least 10 episodes of headache occurring on <1 day per month on average (<12 days per year) and fulfilling criteria B-D | | |
| B. Lasting from 30 minutes to 7 days | | |
| C. At least two of the following four characteristics: | | |
| 1. bilateral location | | |
| 2. pressing or tightening (non-pulsating) quality | | |
| 3. mild or moderate intensity | | |
| 4. not aggravated by routine physical activity such as walking or climbing stairs | | |
| D. Both of the following: | | |
| 1. No nausea or vomiting | | |
| 2. No more than one of photophobia or phonophobia | | |
| E. Not better accounted for by another ICHD-3 diagnosis | | |
| **Cluster Headache:** | | |
| A. At least five attacks fulfilling criteria B–D | | |
| B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated) | | |
| C. Either or both of the following: | | |
| 1. At least one of the following symptoms or signs, ipsilateral to the headache: | | |
| a) conjunctival injection and/or lacrimation | | |
| b) nasal congestion and/or rhinorrhoea | | |
| c) eyelid oedema | | |
| d) forehead and facial sweating | | |
| e) forehead and facial flushing | | |
| f) sensation of fullness in the ear | | |
| g) miosis and/or ptosis | | |
| 2. a sense of restlessness or agitation | | |
| D. Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active | | |
| E. Not better accounted for by another ICHD-3 diagnosis. | | |

| | | |
|---|---|---|
| **Paroxysmal Hemicrania:** | | |
| A. At least 20 attacks fulfilling criteria B-E | | |
| B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2–30 minutes | | |
| C. At least one of the following symptoms or signs, ipsilateral to the pain: | | |
| 1. conjunctival injection and/or lacrimation | | |
| 2. nasal congestion and/or rhinorrhoea | | |
| 3. eyelid oedema | | |
| 4. forehead and facial sweating | | |
| 5. forehead and facial flushing | | |
| 6. sensation of fullness in the ear | | |
| 7. miosis and/or ptosis | | |
| D. Attacks have a frequency above five per day for more than half of the time | | |
| E. Attacks are prevented absolutely by therapeutic doses of indomethacin | | |
| F. Not better accounted for by another ICHD-3 diagnosis. | | |
| **Short-lasting unilateral neuralgiform headache attacks:** | | |
| A. At least 20 attacks fulfilling criteria B–D | | |
| B. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal and/or other trigeminal distribution, lasting for 1–600 seconds and occurring as single stabs, series of stabs or in a saw tooth pattern | | |
| C. At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain: | | |
| 1. conjunctival injection and/or lacrimation | | |
| 2. nasal congestion and/or rhinorrhoea | | |
| 3. eyelid oedema | | |
| 4. forehead and facial sweating | | |
| 5. forehead and facial flushing | | |
| 6. sensation of fullness in the ear | | |
| 7. miosis and/or ptosis | | |
| D. Attacks have a frequency of at least one a day for more than half of the time when the disorder is active | | |
| E. Not better accounted for by another ICHD-3 diagnosis. | | |

| | | |
|---|---|---|
| **Hemicrania Continua:** | | |
| A. Unilateral headache fulfilling criteria B-D | | |
| B. Present for >3 months, with exacerbations of moderate or greater intensity | | |
| C. Either or both of the following: | | |
| 1. At least one of the following symptoms or signs, ipsilateral to the headache: | | |
| a) conjunctival injection and/or lacrimation | | |
| b) nasal congestion and/or rhinorrhoea | | |
| c) eyelid oedema | | |
| d) forehead and facial sweating | | |
| e) forehead and facial flushing | | |
| f) sensation of fullness in the ear | | |
| g) miosis and/or ptosis | | |
| 2. A sense of restlessness or agitation, or aggravation of the pain by movement | | |
| D. Responds absolutely to therapeutic doses of indomethacin | | |
| E. Not better accounted for by another ICHD-3 diagnosis. | | |
| **Primary cough headache:** | | |
| A. At least two headache episodes fulfilling criteria BD | | |
| B. Brought on by and occurring only in association with coughing, straining and/or other Valsalva manoeuvre | | |
| C. Sudden onset | | |
| D. Lasting between 1 second and 2 hours | | |
| E. Not better accounted for by another ICHD-3 diagnosis. | | |
| **Primary exercise headache:** | | |
| A. At least two headache episodes fulfilling criteria B and C | | |
| B. Brought on by and occurring only during or after strenuous physical exercise | | |
| C. Lasting <48 hours | | |
| D. Not better accounted for by another ICHD-3 diagnosis. | | |
| **Primary headache associated with sexual activity:** | | |
| A. At least two episodes of pain in the head and/or neck fulfilling criteria B-D | | |
| B. Brought on by and occurring only during sexual Activity | | |
| C. Either or both of the following: | | |
| 1. Increasing in intensity with increasing sexual excitement | | |
| 2. Abrupt explosive intensity just before or with Orgasm | | |
| D. Lasting from 1 minute to 24 hours with severe intensity and/or up to 72 hours with mild intensity | | |
| E. Not better accounted for by another ICHD-3 diagnosis. | | |

| | | |
|---|---|---|
| **Cold Stimulus Headache:** | | |
| A. At least two acute headache episodes fulfilling criteria B and C | | |
| B. Brought on by and occurring only during application of an external cold stimulus to the head | | |
| C. Resolving within 30 minutes after removal of the cold stimulus | | |
| D. Not better accounted for by another ICHD-3 diagnosis. | | |
| **Primary Stabbing Headache:** | | |
| A. Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B–D | | |
| B. Each stab lasts for up to a few seconds | | |
| C. Stabs recur with irregular frequency, from one to many per day | | |
| D. No cranial autonomic symptoms | | |
| E. Not better accounted for by another ICHD-3 diagnosis. | | |
| **Nummular Headache:** | | |
| A. Continuous or intermittent head pain fulfilling criterion | | |
| B. Felt exclusively in an area of the scalp, with all of the following four characteristics: | | |
| 1. sharply contoured | | |
| 2. fixed in size and shape | | |
| 3. round or elliptical | | |
| 4. 1–6 cm in diameter | | |
| C. Not better accounted for by another ICHD-3 diagnosis. | | |
| **Hypnic Headache:** | | |
| A. Recurrent headache attacks fulfilling criteria B-E | | |
| B. Developing only during sleep, and causing Wakening | | |
| C. Occurring on ≥10 days per month for >3 months | | |
| D. Lasting ≥15 minutes and for up to 4 hours after Waking | | |
| E. No cranial autonomic symptoms or restlessness | | |
| F. Not better accounted for by another ICHD-3 diagnosis. | | |
| **New daily persistent headache (NDPH):** | | |
| A. Persistent headache fulfilling criteria B and C | | |
| B. Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours | | |
| C. Present for >3 months | | |
| D. Not better accounted for by another ICHD-3 diagnosis. | | |

# APPENDIX III: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr EC Steyn

## HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
## CLEARANCE CERTIFICATE NO. M170714

| | |
|---|---|
| **NAME: (Principal Investigator)** | Dr EC Steyn |
| **DEPARTMENT:** | School of Clinical Medicine<br>Division of Neurology<br>Charlotte Maxeke Johannesburg Academic Hospital |
| **PROJECT TITLE:** | Sensitivity and specificity of fundoscopy in determining the need for brain-computed tomography in patients presenting with new onset headache |
| **DATE CONSIDERED:** | 28/07/2017 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Professor G Modi |
| **APPROVED BY:** | Professor PE Cleaton-Jones, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 20/12/2017 |

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

**DECLARATION OF INVESTIGATORS**

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

Principal Investigator Signature — Date: 20/12/2017

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

# APPENDIX IV: PLAGIARISM REPORT

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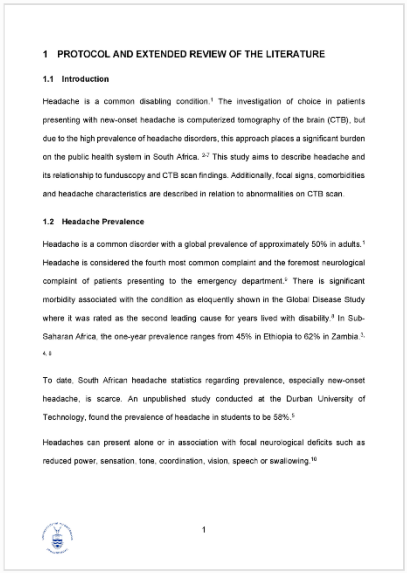

1 PROTOCOL AND EXTENDED REVIEW OF THE LITERATURE

1.1 Introduction

Headache is a common disabling condition.[1] The investigation of choice in patients presenting with new-onset headache is computerized tomography of the brain (CTB), but due to the high prevalence of headache disorders, this approach places a significant burden on the public health system in South Africa. [2-7] This study aims to describe headache and its relationship to funduscopy and CTB scan findings. Additionally, focal signs, comorbidities and headache characteristics are described in relation to abnormalities on CTB scan.

1.2 Headache Prevalence

Headache is a common disorder with a global prevalence of approximately 50% in adults.[1] Headache is considered the fourth most common complaint and the foremost neurological complaint of patients presenting to the emergency department.[2] There is significant morbidity associated with the condition as eloquently shown in the Global Disease Study where it was rated as the second leading cause for years lived with disability.[3] In Sub-Saharan Africa, the one-year prevalence ranges from 45% in Ethiopia to 62% in Zambia.[1, 4, 8]

To date, South African headache statistics regarding prevalence, especially new-onset headache, is scarce. An unpublished study conducted at the Durban University of Technology, found the prevalence of headache in students to be 58%.[9]

Headaches can present alone or in association with focal neurological deficits such as reduced power, sensation, tone, coordination, vision, speech or swallowing.[10]

1

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ORIGINALITY REPORT

| 3% | 0% | 2% | 2% |
|---|---|---|---|
| SIMILARITY INDEX | INTERNET SOURCES | PUBLICATIONS | STUDENT PAPERS |

PRIMARY SOURCES

| | | |
|---|---|---|
| 1 | "Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition", Cephalalgia, 2018<br>Publication | 1% |
| 2 | Schankin, Christoph J., Fabian Kästele, Lisa Ann Gerdes, Tobias Winkler, Endy Csanadi, Tobias Högen, Hannah Pellkofer, Walter Paulus, Tania Kümpfel, and Andreas Straube. "New-Onset Headache in Patients With Autoimmune Encephalitis Is Associated With anti-NMDA-Receptor Antibodies : Headache", Headache The Journal of Head and Face Pain, 2016.<br>Publication | 1% |
| 3 | Beau Bruce. "Nonmydriatic Ocular Fundus Photography in the Emergency Department: How It Can Benefit Neurologists", Seminars in Neurology, 2015<br>Publication | 1% |
| 4 | Submitted to University of South Africa<br>Student Paper | 1% |

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