THE FREQUENCY OF CEREBELLAR TONSILLAR ECTOPIA IN PRIMARY HEADACHE PATIENTS

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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

I, Saiesha Arti Dindayal, do hereby declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in the division of Neurology. This research report is submitted in the publishable format as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted for any other examination or degree at this or any other University.

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The …28…. day of ……May…… 2019

II. Dedication

To my mom, brother, husband and in-laws for their unwavering support.

III. Presentations originating from this research

- Oral Presentation at the Combined Neurosciences Academic Meeting, University of the Witwatersrand, Johannesburg, 6 August 2018.
- Poster presentation at the joint congress of the Neurological Association of South Africa (NASA) and African Academy of Neurology (AFAN), 1 March 2019.

IV. Ethical considerations

Permission for this retrospective 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 – M170369).

V. Abstract

Background: The frequency of cerebellar tonsillar ectopia (TE) has not been adequately quantified in the headache population to date.

Aims: To determine the frequency of TE (both borderline tonsillar ectopia [BTE] and Chiari 1 malformation (CM-1)) in patients with primary headache disorder. To compare the frequency of tonsillar ectopia to the estimated frequency reported in the general population.

Methods:

The records of 299 adult (≥18yrs) patients with primary headache and magnetic resonance images (MRI) of the brain were retrospectively reviewed and directly examined for the lowest cerebellar tonsillar position. Patients were stratified according to lowest tonsillar position into 3 groups; normal, BTE and CM-1. Secondary causes of tonsillar ectopia were excluded. Frequency tables were computed and reported.

Results: Of the 299 patients with primary headache disorder there were, 14 BTE (4.7%) , 3 CM-1 (1%) and 282 (94.3%) normal category patients .

The frequency of BTE in primary headache patients was 4.7% and is of statistical significance ($p= 0.004$) when compared to a neuroradiological series. The frequency of CM-1 in primary headache patients compared to that reported in the general population showed no significant difference between them ($p>0.05$).

Conclusion: 94.3% of primary headache patients had normal MRI brain scans. We do not advocate investigating patients with isolated primary headache for tonsillar ectopia. BTE may affect pain modulation in severe headaches.

VI. Acknowledgements

- I am especially grateful to Professor Modi for his guidance as my supervisor and making this research possible
- To all the radiologists at the Life Brenthurst clinic in Parktown for their time reporting on the magnetic resonance images.

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ABBREVIATIONS:

ADC	Apparent diffusion coefficient
AD	Axial diffusivity
BOD	Bone-only decompression
BTE	Borderline tonsillar ectopia
CDH	Chronic daily headache
CM	Chiari malformation
CM-1	Chiari type 1 malformation
CMH	Headache attributed to Chiari malformation type 1
CSF	Cerebrospinal fluid
CT	Computed tomography
DTI	Diffusion tensor imaging
ESR	Erythrocyte sedimentation rate
FMD	Foramen magnum decompression with duraplasty
FA	Fractional anisotropy
ICHD-3	The International classification of headache disorders, 3rd edition
MRI	Magnetic resonance imaging
PAG	Periaqueductal grey matter
RD	Radial Diffusivity
TAC	Trigeminal autonomic cephalalgia
TE	Tonsillar ectopia (cerebellar)
TTH	Tension type headache

Chapter 1: Protocol and Extended Review of the literature

1.1 Introduction

Chronic headaches are common and lead to significant distress and functional impairment.[1] Certain medical conditions are associated with a higher frequency of headaches.[2] Borderline cerebellar tonsillar ectopia (BTE) which may be defined as the downward displacement of the cerebellar tonsils <5 mm below the foramen magnum detected on magnetic resonance imaging (MRI) and Chiari type 1 malformation (CM-1) defined as downward displacement of cerebellar tonsils ≥ 5mm below the foramen magnum detected on MRI are among these conditions.[2,3] Although questions still persist about the clinical significance of this entity on headache, patients with cerebellar tonsillar ectopia (BTE + CM-1) have a higher frequency of headache (30-81%) than the general population and severe headache has been reported in 16% of patients.[2,4,5] Patients with CM-1 and BTE are known to present with a spectrum of headache disorders. Few studies have described the relationship between primary headache disorders and CM-1, even fewer have included BTE.[6]

1.2 Headache

1.2.1 Headache Background

Headache is the most common presenting complaint in general and neurological consultation.[7] The global prevalence of headache in the adult population is estimated at 46%.[1,8] South African epidemiology is however unknown. Headache can be the presenting feature of both benign as well as serious conditions.[7] When evaluating a headache it is therefore important to differentiate primary from secondary headaches.[8]

Primary headaches are those where there is no underlying cause identifiable, headache is part of the phenotype of the syndrome. Secondary headaches are those where head pain is a

symptom of an underlying causative disorder.[9] Approximately 90% of headaches seen in practice are of the primary variety, and less than 10% are of the secondary variety.[10,11,12] While primary headache disorders are more common, it is important to rule out secondary causes which may have implications for management and prognosis.[7,8] Even though primary headaches are thought to be benign they are associated with significant morbidity.[1]

1.2.2 Classification of headache

The International Classification of headache Disorders, 3rd Edition (ICHD-3) classifies headaches as follows: [11]

Primary Headaches:

1. Migraine
2. Tension Type headaches
3. Trigeminal autonomic cephalalgias
4. Other primary headache disorders

Secondary Headaches:

1. Headache attributed to trauma or injury to the head or neck
2. Headache attributed to cranial or cervical vascular disorders
3. Headache attributed to nonvascular intracranial disorders
4. Headache attributed to substance or its withdrawal
5. Headache attributed to infection
6. Headache attributed to disorder of homeostasis
7. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth mouth or other cervical structure
8. Headache attributed to psychiatric disorder.[11]

1.2.2.1 Migraine

Migraines are the most common severe primary headache disorder with an estimated global prevalence of 11%. Attacks last 4-72 hours and are characterized by a unilateral throbbing pain that builds up insidiously and is of moderate to severe intensity which may be accompanied by nausea and/or vomiting, photophobia and/or phonophobia. Migraine may or may not be preceded or accompanied by aura.[8, 11]

1.2.2.2 Tension type headache (TTH)

Tension type headaches are the most common primary headache disorder with an estimated global prevalence of 42%. They are characterized by a bilateral pressing or tightening pain of mild to moderate intensity that is not aggravated by physical activity and lasts minutes to days.[8, 11]TTH is not accompanied or preceded by aura.

1.2.2.3 Trigeminal Autonomic cephalalgias (TACs)

TACs are primary headache syndromes characterized by severe, short-lasting, unilateral head pain typically associated with paroxysmal facial autonomic symptoms such as rhinorrhoea, lacrimation and components of Horner's syndrome. TACs include cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headaches and hemicrania continua. These are differentiated by duration and frequency of attacks. Cluster headache is the most common TAC.[8,11]

The global prevalence of cluster headache is 0.1%. Cluster headache is characterized by severe attacks of unilateral pain in the orbital, supraorbital, or temporal regions lasting 15 to 180 minutes. The pain may be accompanied by ipsilateral conjunctival injection, tearing, nasal congestion, rhinorrhea, facial swelling, miosis, ptosis and restlessness or agitation.[8,11]

1.2.2.4 Other primary headache disorders

The headache disorders in this chapter of the ICHD-3 (beta) can be grouped into four categories: [11]

(1) Headaches associated with physical exertion:

- Primary cough headache
- Primary exercise headache
- Primary headache attributed to sexual activity
- Primary thunderclap headache

(2) Headaches attributed to direct physical stimuli

- Cold-stimulus headache
- External-pressure headache

(3) Epicranial headaches (i.e. head pain over the scalp)

- Primary stabbing headache
- Nummular headache

(4) Other miscellaneous primary headache disorders

- Hypnic headache
- New daily persistent headache[11]

This category in the ICHD-3 comprises of a number of clinically heterogeneous primary headache disorders. The ICHD-3 notes that the pathogenesis of these conditions are still poorly understood, and that treatments are based on case reports or uncontrolled trials. The characteristics of headache in this group can be mimicked by underlying pathology i.e. secondary headaches. The diagnosis of a primary headache disorder in this category is usually on the basis of exclusion. For this reason this category of primary headache disorder will be excluded from our study.[11]

1.2.3 Headache Diagnosis

Primary headache disorders are diagnosed by detailed history, pattern recognition, a noncontributory neurological examination, and in some instances by exclusion of a secondary cause.[7, 11] Usually the diagnosis of a primary headache can be made without diagnostic testing. There are numerous indications for investigating primary headaches and neurologists must make clinical decisions on a case-by-case basis as to whether further investigation for an underlying cause is needed. Secondary headaches are diagnosed when a cause is identified on examination or with investigations such as neuroimaging (Computed tomography (CT) and/or MRI of the brain), lumbar puncture with/without opening pressures or specific biochemical markers e.g. erythrocyte sedimentation rate (ESR).[10] One could argue that neuroimaging is the most important investigation in the diagnosis of secondary headache disorders.

1.2.4 Role of the ICHD-3

The ICHD-3 has the goal of bringing uniformity to headache diagnosis across the globe. The ICHD-3 lays down criteria that needs to be fulfilled for the diagnosis of each entity, however the ICHD-3 criteria remains a useful tool and guideline when uncertainty arises and for research purposes, it does not replace the clinical diagnostic process.[11,12]

The ICHD-3 emphasizes that it does not replace the clinical diagnostic process by including the last criterion for every headache disorder is “not accounted for by another ICHD-3 diagnosis”. According to the ICHD-3 guideline this is there for the consideration of other possible diagnoses as a routine part of the diagnostic process which applies in particular to assessing whether a headache is primary or secondary.[8, 11,12]

The ICHD-3 further states that even when a headache has the characteristics of a primary headache if it occurs in close relation to a disorder known to cause headache then the headache is coded as a secondary headache attributed to the causative disorder. The authors of the ICHD-3 acknowledge that for most secondary headaches the characteristics are poorly described and may overlap or mimic primary headache disorders.[11,12]

In practice clinicians are aware that patients do not always present in a manner that fulfils the criteria described in ICHD-3 beta. Primary headaches may at times present atypically without ICHD-3 criteria being fulfilled, secondary headaches may mimic primary headaches, or both may coexist. These variations in presentation can make headache diagnosis difficult.[12]

1.2.5 The role of neuroimaging in headache diagnosis

Neuroimaging is used to detect intracranial abnormalities that cause headaches.[10, 13] Most authors consider neoplastic disease, hydrocephalus, vascular malformations, Chiari malformation, large arachnoid cysts, intracranial haemorrhage, and acute cerebral infarcts as significant abnormalities that can be detected on neuroimaging and are known to cause headache.[10,13] The rate of detecting significant intracranial abnormalities in patients with headache varies according to methodology used in different studies (e.g. Acute vs nonacute headaches or headaches in patients with normal neurological examination).[10] In the study by Sempere et al, the rate of significant intracranial abnormalities in patients with nonacute headache and normal neurological examination was 0.9%.[13] The proportion of patients with headache and significant lesions is relatively small, but at times clinical features alone cannot differentiate patients that will have significant pathology and those that will not, therefore neuroimaging is an important tool in the investigation of headaches.[13]

The crude prevalence of incidental findings on brain MRI is 2.7%, or one for every 37 neurologically asymptomatic people scanned.[13,14]The detection of incidental brain findings increases when higher resolution MRI sequences are used when compared to studies using standard sequences (4.3% v 1.7%). [14,15]

With some conditions, such as Chiari malformations and pituitary lesions, it may not be possible to say with certainty that the headache is related to the structural lesion.[12] Most neuroimaging series do not include or report on BTE. Furthermore, in a study by Smith et al, of the patients with tonsils 5 mm or more below the foramen magnum, CM was mentioned in the radiology report of only 39 (53%) of 74 patients, therefore unless directly investigated for, 57% of patients with CM-1 with tonsillar ectopia will be missed on routine MRI reporting.[16]

Due to the low detection rate of significant intracranial abnormalities and the high cost of neuroimaging it is not indicated to image every patient with chronic headache in the absence of redflags[17] It has however been shown that neurological consultation and index consultations are associated with a significantly higher rate of neuroimaging utilization . Neurologists may utilize neuroimaging more for several reasons; including the tendency of specialists to see sicker patients with more red flags, perform more detailed clinical histories and examinations that uncover red flags, and patient expectations for testing may be higher when seeing a specialist.[17]

1.2.5.1 Indications for neuroimaging

Red flags for imaging of headaches include:

- New onset, severe headache
- Associated neurologic symptoms or signs (e.g. altered sensorium, weakness, double vision, papilledema, convulsions, localizing neurological signs)
- Immunosuppression (HIV) or cancer
- Nuchal rigidity or meningism
- Older age of onset (> 50 yrs.)
- Headache precipitated by exertion or Valsalva
- Hyperacute onset headache i.e. thunderclap headache
- Systemic symptoms (e.g. fever, weight loss, temporal artery tenderness)
- Progression of headache
- Painful red eye with associated halos around lights
- Trauma to the head and neck
- significant travel history[17]

1.2.5.1.1 Indications for neuroimaging for migraine

There is no indication for neuroimaging in patients with chronic episodic typical migraine except when:

- atypical or protracted or brainstem aura
- side-locked migraine
- migraine with hemiplegia
- migraine as a symptom an underlying condition such as cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes (MELAS)

- migraine onset later in life
- progression of pain[17,18]

1.2.5.1.2 Indication for neuroimaging for tension type headache

Any progression in TTH i.e. worsening of pain intensity or increased frequency of headaches or unremitting pain is an indication for neuroimaging because brain tumours and other forms of secondary headaches can mimic this presentation. Patients with chronic TTH or TTH not responding to treatment should receive cerebral MRI once to exclude further pathology. [18]

1.2.5.1.3 Indication for neuroimaging for TACs

In the past patients with TACs were only investigated if they presented atypically or if an abnormality was found on examination or if the pain was intractable. However, due to the high rate of unexpected findings detected on neuroimaging in patients with TACs, mainly pituitary tumours and paracavernous structural lesions not detectable through clinical examination, neuroimaging is now advised for all patients with TACs. [18]

1.2.5.1.4 Indication for neuroimaging to exclude secondary causes

The heterogeneous entities that are included in Chapter 4 of ICHD-3 as discussed earlier will need neuroimaging as they all are diagnoses of exclusion.[11,12]

1.2.5.1.5 Indication for neuroimaging to alleviate patient anxiety

Often times patients are concerned that their headaches are due to brain tumours or other serious diseases. Sixty percent of patients in a British regional headache clinic were fearful that their headache was due to serious underlying illness. Two-thirds of them were still fearful after consultation, and expressed the desire for neuroimaging. In these circumstances the strong patient desire for clarification can justify the use of neuroimaging.[19]

1.2.5.2 CT vs MRI

Although data regarding the relative sensitivity of MRI compared with CT in headaches is insufficient it is generally agreed that CT is the imaging modality of choice for acute headaches and MRI is preferred for nonacute or recurrent headaches. CT is the imaging modality of choice in acute headaches because of its availability after hours as well as the increased sensitivity in the detection of acute subarachnoid haemorrhage, acute traumatic brain injury, and bony abnormalities. MRI is preferred in the investigation of nonacute headache as it offers greater resolution of the brain parenchyma. It has the added benefit of avoiding radiation due to CT scanning. MRI is more sensitive than CT in the detection of; posterior fossa abnormalities including cerebellar tonsillar ectopia, pituitary pathology, white matter disease, infarcts, dural venous sinus thrombosis, subdural and epidural hematomas, tumours, meningeal infiltration, inflammation or enhancement due to low intracranial pressure, as well as cerebritis and abscesses. MRI is the imaging modality of choice for posterior fossa pathology[10, 18]

1.2.5.3 Neuroimaging: 2 sides to the coin, a balanced approach

Because the complaint of headache is so common in primary care and neurological practice, when ordering neuroimaging for patients with headaches one has to balance two approaches i.e. a patient-tailored approach and a population-based approach to medicine. Physicians must balance evidence-based cost-cutting guidelines and the potential benefit of the individual[20]

Population based guidelines are, however not always consistent with the neurosurgical perspective. For example in patients with brain tumours it was shown that if the American College of Radiology/Consumer Reports recommendations were followed, a diagnostic delay or error would have occurred for 7.4% of patients with isolated headaches and no red flags.[20]

Although patients with headaches do not frequently harbour brain tumours, patients with brain tumours frequently present with isolated headaches. Early diagnosis of brain tumours is preferred for treatment.[20] Strict population based guidelines can negatively affect the management of patients with brain tumors from a neurosurgical perspective[20] From a neurosurgical perspective TE is similar to brain tumours as they are infrequently detected on neuroimaging but frequently present with isolated headaches.

1.3 Cerebellar Tonsillar Ectopia:

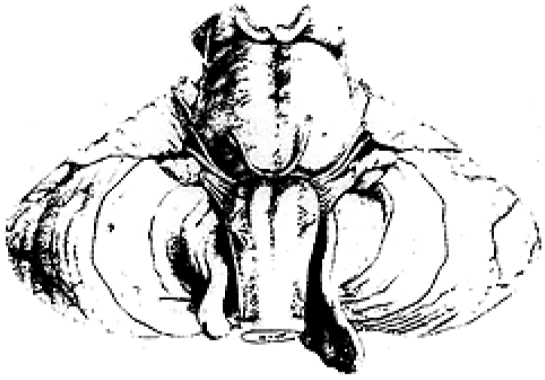

Fig 1. Illustration of Chiari 1 malformation from Chiari's original 1896 publication[24]

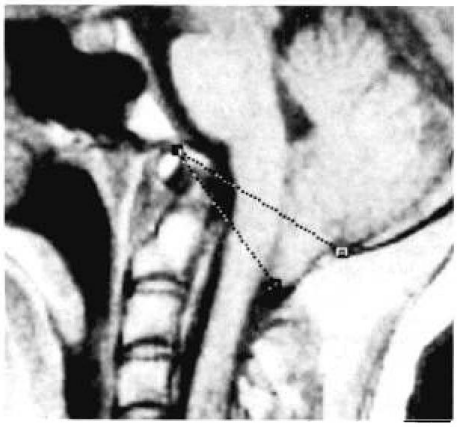

Fig 2. Midsagittal T1 MRI of the brain and cervical spine demonstrating cerebellar tonsillar herniation[24]

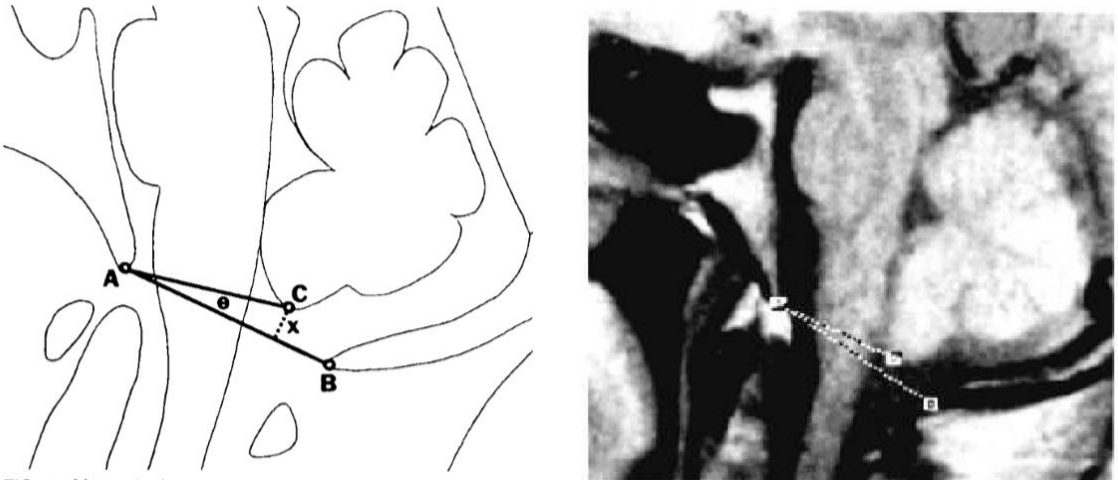

Fig 3. A schematic diagram and MRI demonstrating the method to determine cerbellar tonsil position with relation to the foramen magnum. Point A is the anterior rim of the foramen magnum and point B is the posterior rim of the foramen magnum. Line AB is called the basion opisthon line. Point C is the lowest tonsillar tip. X represents the distance of the tonsil from AB.[24]

1.3.1 Definition:

Cerebellar tonsillar ectopia refers to herniation or descent of the cerebellar tonsils (the paraflocculus) below the foramen magnum.[21, 22]

1.3.1.1 Anatomical Definition:

In 1891-1896 Hans Chiari described a spectrum of 4 types of cerebellar ectopy on the post-mortem of children and adolescents. Chiari originally described the type I malformation as "elongation of the tonsils and medial parts of the inferior lobes of the cerebellum into cone shaped projections which accompany the medulla oblongata into the spinal canal". He did not however quantify the degree of cerebellar herniation.[23] CM-1 is the most common and clinically relevant of the four malformations described, with a high mortality occurring at early ages in types II-IV.[3]

1.3.1.2 Radiological definition:

With the advent of MRI this anatomically pathological entity was translated onto neuroimaging. In 1985 Aboulezz et al studied the position of the cerebellar tonsils with reference to the foramen magnum using MRI. In the 'normal' population (82 patients) tonsillar position ranged from 2.8 mm below the foramen magnum to 20 mm above, whereas in patients with CM (11 patients) the tonsils were found 5.2 to 17.7 mm below the foramen magnum. The authors concluded that the tonsils may extend up to 3 mm below the foramen magnum in the normal population, is borderline between 3mm and 5mm and extension greater than 5mm is clearly pathological and indicative of CM.[24]

Barkovich, et al compared the MRIs of 200 patients with symptoms unrelated to CM-1 to the MRIs of 25 patients with known CM-1. In this study patients with minimal symptoms may have been underestimated or missed. In controls, tonsil position ranged from 8 mm above to 5 mm below the foramen magnum and in the CM patients from 3 to 29 mm below the foramen magnum. The authors stated that, in terms of the most sensitive diagnosis, a herniation 2 mm below the foramen magnum should be the cut-off because no symptomatic patient had less than 3-mm herniation and only one asymptomatic patient had more than 3-mm ectopia. With 2 mm below the foramen magnum taken as the lowest extent for tonsils in normal patients, the sensitivity in predicting symptomatic patients was 100% and the specificity was 98.5% (3 false-positives). When 3 mm below the foramen magnum was used as the lowest normal tonsillar position, the sensitivity was 96% and the specificity was 99.5% [23,25]

Ishikawa studied 53 control patients and found that the cerebellar tonsils were always located at or above the line of the foramen magnum. Chun-Yiu Cheng et found that the cerebellar tonsillar tip in healthy patients was found at an average of 2.8 mm above the basion-opisthion reference line (range, 0–10.5 mm) and concluded that using the current MRI reference

standards, the incidence of tonsillar herniation could be significantly underestimated and any inferior displacement of a tonsil below the foramen magnum should be regarded as abnormal.[23, 26]

Mikulis et al studied the effect of age on tonsillar position using 220 patients (age range 5 months–89 years). It was found that the cerebellar tonsils move upward with advancing age. Based on this the following criteria for CM (pathological ectopia) was suggested: first decade, 6 mm below the foramen magnum; second to third decades, 5 mm; fourth to eighth decades, 4 mm; and ninth decade, 3 mm below the foramen magnum. These criteria were based on the distance greater than two standard deviations from the normal range for each decade.[26]

Table 1: Summary of the evolution of the definition of normal cerebellar tonsillar position and CM-1

Authors	Year	Number of subjects	Normal Definition	CM-1 Definition
Aboulezz	1985	82 asymptomatic 13 CM	<3mm	≥5mm
Barkovich	1986	200 normal 25 CM	≤2mm	≥ 3mm
Ishikawa	1983	50	≤0mm	>0mm
Mikulis	1992	220	0-10yrs < 6mm 20-30yrs < 5mm 40-90yrs < 4mm 90+yrs < 3mm	0-10yrs ≥ 6mm 20-30yrs ≥ 5mm 40-90yrs ≥ 4mm 90+yrs ≥ 3mm

It is generally accepted that displacement of one or both cerebellar tonsils 5 mm or more below the basion-opisthion line (foramen magnum) is the basis for the neuroradiological diagnosis of CM-1 or a borderline position (3–5 mm below the foramen magnum) should be regarded as pathological when accompanied by other elements of the malformation, like syringohydromyelia and/or cervico-medullary kinking. Without accompanying elements of CM or evidence of posterior fossa crowding tonsillar ectopia of 3-5mm below the foramen magnum is considered borderline and less than 3mm is considered normal and of no clinical significance.[3,26] . Most studies have focused on CM-1 due to definition.

However even with this generally accepted definition heterogeneity still exists in the literature as shown in a recent systematic review and summarized in table 2.[27]

Table 2. Different CM definitions used in the literature [27]

Reference	CM-1 Definition Used
Bindal et al.[3]	Herniation of the cerebellar tonsils below the plane of the foramen magnum
Chavez et al.[4]	Herniation of the cerebellar tonsils through the foramen magnum >5 mm
Kalb et al.[14]	Herniation of the cerebellar tonsils through the foramen magnum >5 mm
Killeen et al.[5]	Herniation of the cerebellar tonsils through the foramen magnum >5 mm
Klekamp et al.[6]	Herniation of the cerebellar tonsils through the foramen magnum >5 mm
Leu[7]	Herniation of the cerebellar tonsils through the foramen magnum >5 mm
Massimi et al.[8]	Not defined
McDonnell et al.[9]	Not defined
Miele et al.[10]	Herniation of the cerebellar tonsils through the foramen magnum >5 mm, posterior fossa crowding, and restricted cerebrospinal fluid flow through the foramen magnum
Morris et al.[11]	Not defined
Nishizawa et al.[15]	Not defined
Ramón et al.[12]	Displacement of the cerebellar tonsils at least 3—5 mm below the foramen magnum; the authors state that the criteria for Chiari 1 malformation should not be considered absolute
Santoro et al.[16]	Not defined
Schneider et al.[17]	Herniation of the cerebellar tonsils through the foramen magnum >5 mm
Schuster et al.[13]	Tonsillar ectopia located below the foramen magnum

For the purpose of this study we will use:

Normal: tonsillar ectopia < 3mm below the foramen magnum

BTE: tonsillar ectopia of 3mm to < 5mm below the foramen magnum

CM-1: tonsillar ectopia ≥ 5mm below the foramen magnum[3]

Using < 3mm i.e. 2mm as the lowest position of normal gives a sensitivity of 100 % for symptomatic tonsillar ectopia with a specificity of 98.5% according to Barkovich et al. [25]

1.3.2 Epidemiology:

The estimated prevalence of CM-1 found in neuroradiologic series is 0.5%-3.5% in general, 0.56%- 0.77% on MRI studies and 0.62% in anatomical dissection studies. The precise prevalence in the general population is unknown.[28] Most series have reported slight female predominance (2-3:1).[22, 29] The prevalence of BTE on MRI, to my knowledge has not been reported.[3] However in the series by Aitken et al, BTE (defined in the study as 2-4 mm) was noted in 19 patients of 5248 patients with MRI scans, or 0.4% of all the head and spine magnetic resonance imaging reviewed in the study.[5]

1.3.3 Cerebellar Tonsil Morphology and other radiological features

The ascent of the cerebellar tonsils with advancing age as demonstrated by Mikulis et al. showed two peaks of acceleration. The first corresponded to late childhood/ adolescence and the second to the last decades of life.[29] It was postulated that in the later decades of life tonsillar ascent is linked to neuronal dropout and brain atrophy which may pull the cerebellar tonsils upwards.[26]

Smith et al reported that in most cases (84%), the right and left tonsils are symmetric with respect to the foramen magnum. However, when tonsillar position was asymmetrical a lower

right tonsil was more common than left (11% vs 4%). Asymmetry increased with lower tonsillar position. The significance of these findings is however unknown.[16]

1.3.4 Cause and Pathophysiology

Chiari malformation is a developmental abnormality of the hindbrain that results in brain tissue extending into the upper end of the spinal canal. It is thought that embryologically there is a primary paraxial mesoderm insufficiency which results in an underdeveloped occipital somite and hence an underdeveloped occipital bone which leads to a smaller volume of the posterior fossa. The skull closure occurs after the brain has formed neural folds. The Chiari malformation then occurs by herniation into the spinal canal due to overcrowding of the posterior fossa. This has been shown in experimental models.[26]

Inheritance is thought to be multifactorial, a discrete genetic cause is unlikely to be found and.[16] Hereditary factors do however play a significant role with 100% concordance in monozygotic triplets and demonstration by Furuya et al that the median position of cerebellar tonsils tend to be higher in the Japanese as compared to Caucasian populations.[16,21] To my knowledge there are currently no African studies reflecting median tonsillar position.

Tonsillar ectopia may also be acquired. Tonsillar ectopia can occur secondary to raised intracranial pressure, which is explained by the Monro-Kellie doctrine. Because the skull is a fixed volume, tonsillar herniation occurs if the cranial cavity volume is reduced e.g. Paget's disease or the volume of the intracranial contents is increased eg brain tumour.[30] Tonsillar ectopia also occurs with low intracranial pressure- due to low CSF volume the cerebellum is less buoyant and the tonsils may sag into the spinal canal. Acquired TE resolves once the cause has been treated. Acquired TE can be readily diagnosed by features in the patient's history and on neuroimaging. [30,31]

1.3.5 Clinical features

CM-1 manifests in numerous ways. Headaches and paraesthesia are the most common presenting symptoms. Symptoms may be caused by spinal cord or brainstem compression or complications of a syrinx as a result other common presenting symptoms include nausea, dysphagia, drop attacks, apnoea, stiffness due to spasticity, ataxia, vertigo, wasting, and dysphonia.[27]

CM-1 may also be asymptomatic and only found incidentally on MRI.[5]

Despite tonsillar ascent with increasing age CM-I typically presents in adolescence or adulthood. The mean age of presentation is 35.9 ± 16.8 years, however it is now commonly diagnosed in children due to the availability of MRI.[16]

Older age at diagnosis is a predictor for more severe symptoms and headache occurrence. In adult series only 14-30% of patients are asymptomatic whereas in series of children 37-57% are asymptomatic at the time of MRI diagnosis.[5]

By radiological definition mild tonsillar ectopia < 5mm is considered to be of no clinical relevance however patients with tonsillar ectopia < 5mm have been reported to present with the same symptoms as CM-I namely headache, neck pain, vertigo, dizziness, gait ataxia, visual changes, limb weakness, tinnitus and tremor .[3,21] Some symptomatic cases have even improved with surgery.[21]

1.3.6 Diagnosis

The diagnosis of CM-1 is based on the radiological definition discussed. Magnetic resonance (MRI) currently represents the best imaging modality for diagnosis.[27] Secondary causes of increased or decreased intracranial pressure should be excluded, as discussed, before TE is reported as CM i.e. primary or developmental.[27]

1.3.7 Definitions and Clinical Correlates:

Strict adherence to the radiologic definitions are not useful clinically as patients classified as radiologically normal or borderline may present with classic neurologic signs and symptoms as well as syringomyelia associated with CM-1 that are amenable to neurosurgical intervention.[3,21] Furthermore 14-30% of patients with CM-1 may be asymptomatic.[5] The use of a discrete 5-mm cut-off for a clinical syndrome is flawed.[16]

There is consensus in the literature that although the current Chiari classification is useful in categorizing patients,[32, 23] "The radiological criteria for tonsillar herniation are not absolute and should be considered within the clinicopathological context".[16,33] Current definition may not represent a continuum of the same disease.[23]

With newer imaging modalities available, more research is being done to try to understand the significance of cerebellar tonsillar ectopia found on MRI to explain the clinicoradiological mismatch.

Due to current definition most research has ignored BTE or included it in control groups. It is for this reason that our study will include and focus on BTE instead of just CM-1.

1.3.8 Management

Patients with clear symptomatology of CM-1 are treated surgically. Clear symptomatology of CM-1 is considered to be signs and symptoms that localize to the craniocervical junction i.e. ataxia, lower cranial neuropathies, spasticity, severe neck pain.[34]

For patients with symptoms of CM-I but who have no signs e.g. patients with headaches, vertigo or nausea, management has been controversial.[34]

Recent literature has clarified some indications for surgery in patients with CM-1 and headache. Migraine like headaches or mild headaches should be managed medically due to

high rate of reported recurrence post surgery.[5,35] Only patients with occipital headaches that fulfil criteria for "Headache attributed to Chiari malformation type 1", ICHD-3(beta) should be treated surgically.[11]

At present, there are two surgical methods for CM-1, both involve posterior fossa decompression. Foramen magnum decompression with duraplasty (FMD) relieves the pressure around the foramen magnum and enlarges the surface of the dura. Bone only decompression (BOD) removes the posterior fossa bones to allow for more space of the hindbrain structures. FMD is currently favoured over BOD however the choice between the two techniques is also controversial.[30]

Despite the above recommendations there is still uncertainty in practice in CM-1 management. In a survey of neurosurgeons, only 46% opted to operate if confronted with a patient with occipital headache as the only symptom, in the absence of syringomyelia even though 67-100% of patients with suboccipital headache were reported to benefit from surgery.[4] Some centres have found that many patients receive inappropriate surgical indication.[36]

In a review of surgical case series by Arnautovic et al it was found that only 1 publication was from Africa and 79% from the United States and Europe.[28,37] With only 1 African publication it is not clear what the South African consensus on the management of Chiari malformation or tonsillar ectopia is, and whether it is any different from internationally accepted practice.[37]

1.3.9 Natural history and Prognosis

Mildly symptomatic and asymptomatic patients with CM-1 is relatively benign and non progressive. Mild headaches and nausea in CM-1 patients treated conservatively tended to improve. Patients with ataxia and sensory disturbances did however not improve when treated conservatively.[27]

1.4 Headache and Cerebellar tonsillar ectopia

1.4.1 Background

Headache is the most common symptom (30-81%) in both patients with CM-1 and BTE. A frequency greater than the general population. Sixteen percent of BTE patients experience severe headache.[3, 4,5, 21]

Patients with CM-1 and BTE experience a spectrum of headache disorders; primary headaches as well a particular type of occipital headache now classified by the ICHD-3 beta as Headache attributed to CM-1.[36]

1.4.2 Headache attributed to Chiari malformation type 1 (CMH):

Headache considered to be caused by CM-1 is described by the ICHD-3 as occipital or suboccipital in location, of less than 5 minutes duration and precipitated by cough or other Valsalva-like manoeuvres. The headache should present in temporal relation to CM-1 or its discovery. The headache should resolve within 3 months after successful treatment of CM-1. The headache can be associated with other known symptomatology of CM-1.[11]

The availability of MRI has shown that CM-1 is the most common cause of cough headache, prior to MRI cough headache was thought to be predominantly primary in nature.[18]

Whilst the ICHD-3 criteria for CMH has provided clarity on indications for surgery for patients with headache and CM-1 studies have shown that CMH is relatively rare in patients with CM-1. Using the ICHD II Toldo et al found that only 27% of children with CM-1 had headache attributed to CM-1 and Pascual found a similar result of 28% .[4,38] Aitken reported that 5% of BTE patients had occipital headache worse on Valsalva.[5] This does not adequately explain the high rate of headache recurrence in patients with TE.

1.4.2.1Pathophysiology of CMH

Cine Phase contrast MRI has been fundamental in the understanding of the pathophysiology of CMH. Cine phase-contrast MRI is a method that allows direct anatomic depiction of moving structures to study the dynamic effects on the CSF flow through the foramen magnum.[39-41]

In normal individuals the systolic arterial pulsation within the cranial cavity produces a slight pulsatile movement of the brain. This pulsatile movement is most pronounced in the diencephalon and brain stem which causes a CSF wave that travels from the basal cisterns into the cervical subarachnoid space. The presence of cerebellar tonsillar ectopia distorts the normal flow dynamics at the craniocervical junction.[41]

In patients with CM, cine phase-contrast MRI detected abnormal pulsatile motion of the cerebellar tonsils, which resulted in selective obstruction of CSF flow from the basal cisterns to the spinal subarachnoid space. The amplitude of the tonsillar pulsation and the severity of the obliteration of the arachnoid space were associated with cough-strain headaches. [27,39- 41]

During cough and Valsalva-like manoeuvres the cerebellar tonsils herniate further into the spinal canal due to the transient dissociation between intracranial and intraspinal pressure gradients, this causes compression of the C1 and C2 roots, pain sensitive meninges and vessels which leads to the specific short duration occipital or suboccipital type of headache.[22, 38] The degree of tonsillar descent correlated with the presence of cough headache in the series by Pascual et al.[22, 39,40]

1.4.3 Primary headaches and cerebellar tonsillar ectopia

Migraines with and without aura, migraines with prolonged aura, basilar migraines, tension type headaches and chronic daily headache have all been reported in patients with TE.[6] The challenge to many medical providers is still whether these headaches are related to TE; if not

causally does CM-1 influence or worsen established primary headaches or are the two entities merely co incidental.[34]

Few studies have described the relationship between migraines and CM-1 and fewer describe the relationship between headaches and borderline tonsillar ectopia. Studies that have investigated this relationship have used the current definition of CM-1 with some inconsistency and described headache types in small groups of patients with differing results.

In Toldo's series (12 BTE patients and 33 CM-1 patients) headache was reported in 64% of patients, all BTE patients with headache (5 patients) had primary headache and 14 of 33 CM-1 patients had primary headache .[4] In Pascual's series of 50 CM-1 patients, 25 (50%) had headache, 11 patients had tension-type headache and five had migraine (12% and 10% of total). The remaining 14 headache patients had CMH.[38] These studies reported the incidence of migraine and tension-type headache to be in accord with that reported in the general adult population.[4, 38]

In Stovner's series of 34 patients with CM-I; 20 reported headache (59%). Eleven of 14 patients suffering from long lasting but not continuous headache met the minimal IHCHD criteria for migraine without aura. Although the frequency of migraine was reported to be similar to general population the proportion of continuous headache in Stovner's series (24%) is higher than the expected prevalence of CDH in the general population (4% to 5%, up to 9% in middle-aged women).[39]

Kaplan et al reported the frequency of episodic migraine to be similar to the general population but found a threefold increase in frequency of chronic migraine in CM-1 patients. Furthermore, chronic daily headache presented at an earlier age and with an increased frequency and pain intensity that was significantly higher in patients with CM-1.In addition,

these patients had symptoms (nausea, vomiting and pain) that were worsened by physical activity.[6]

1.4.3.1 Migraine pathophysiology and Cerebellar Tonsillar ectopia

Questions have been raised as to whether the pathogenesis of TE and migraine may be linked.[6]

Pathogenesis of migraine:

Primary neuronal and glial dysfunction results in a self-propagating wave that spreads across the cerebral cortex or cerebellum or hippocampus[42] This is also known as cortical spreading depression of Leão. Migraine without aura may be caused by cortical spreading depression in areas of the brain (cerebellum and hippocampus) where depolarization is not consciously perceived.[6,42,43]

The depolarizing wave travels across the cortex releasing nitric oxide, arachidonic acid, protons ,and potassium extracellularly. This activates matrix metalloprotease which affects the permeability of the blood brain barrier causing activation of the meningeal nociceptors. The meningeal nociceptors are innervated by the trigeminal nerve anteriorly and C1 and C2 posteriorly. The trigeminovascular reflex is activated. This is called peripheral sensitization. Trigeminal neurons (first order neurons) release calcitonin gene-related peptide, substance P, and neurokinin A leading to vessels dilatation and the extravasation of plasma proteins called sterile neurogenic inflammation. There is convergence of the projections from the upper cervical nerve roots and the trigeminal nerve (the first order neurons) at the trigeminal nucleus caudalis. Convergence explains the anterior and posterior distribution of head pain as well neck pain.[42,43]

Second order neurons then ascend from the trigeminal nucleus caudalis to the thalamus and primary sensory cortex (central sensitization).Second-order neurons from the trigeminal nucleus caudalis also project to the mesencephalic trigeminal complex, the reticular formation, the cerebellum and the midbrain and pontine parabrachial nuclei. Brainstem nuclei are important is descending pain pathways which modulate pain as well as relaying pain signals to limbic regions involved in the emotional responses to pain.[42,43]

Sensitization refers to the process in which neurons become increasingly responsive to nociceptive and non-nociceptive stimulation.[42,43]

Central sensitization can be modulated by projections from the rostral trigeminal nuclei, the periaqueductal grey, and the nucleus raphe magnus as well as by descending cortical inhibitory systems.[42,43]

Many symptoms of migraine including the throbbing quality of the pain, the worsening of pain with coughing, bending, or sudden head movements and hyperalgesia may be explained by sensitization. These symptoms bear similarity with features of CMH. [42,43]

The cerebellum is increasingly recognized in the pathophysiology of migraine. The cerebellum plays a role in non-apparent aura and pain modulation, the brainstem also has an important role in pain modulation and sensitization, C1 and C2 mediate pain from the occiput. These structures are common to TE.[6]

Few reports have described a connection between the pathophysiology of migraine and TE.[6] Newer imaging modalities have shown possible links between the 2 entities.

MRI studies identified changes consistent with iron deposition in the periaqueductal grey (PAG) area in subjects with episodic migraines and CM. Repeated central sensitization or repetitive activation at the level of the PAG, is associated with high iron turnover and

progressive free radical-mediated permanent neuronal PAG damage. The PAG receives afferents from the trigeminal nucleus caudalis and is a vital component in the modulation of descending inhibitory pathways.[6]

Diffusion tensor imaging (DTI) is a non-invasive imaging modality that can identify microstructural pathological alterations such as the axonal or myelin damage by quantitatively assessing water diffusion in tissues in relation to isotropic and anisotropic diffusion. This is because diffusion properties of white matter changes as a result of microstructural damage.[44]

DTI parameters:

- Apparent diffusion coefficient (ADC) measures the total water diffusion within selected tissue.
- Fractional anisotropy (FA) reflects fibre tract structural integrity and the degree of orientation of cellular structures within them.
- Axial diffusivity (AD) measures water diffusivity along the main axis of diffusion within a voxel, and shows the coherence of fibres and structure of axonal membranes. AD is a marker for axonal damage
- Radial diffusivity (RD) is defined as the mean magnitude of water diffusion perpendicular to the axons. RD is a marker for demyelination.[44]

It was found that ADC and AD are increased in patients with BTE compared to controls at the level of the pons and medial lemniscus. ADC and AD at the level of the pons and medulla were increased in patients with CM-1 as compared to borderline tonsillar ectopia and FA was increased at the level of the pons and medulla in CM-1 as compared to BTE patients. DTI parameters have shown increased features of microstructural changes in the brainstem of patients BTE and CM-1 when compared to controls.[44]

These finding provide evidence that support that there are microstructural changes occurring in the brainstem in patients with BTE and CM-1 which may support theories of increased central pain sensitization and reduced pain modulation in patients with CM-1 and BTE and primary headache disorders.[44]

1.4.4 Headaches and Cerebellar tonsillar ectopia: current view

Kaplan et al concluded in their paper that CM-1 may be a factor associated with chronic migraine. It was suggested that larger prospective studies are needed to clarify the relationship.[6]

Currently there is however, no evidence suggesting that CM-1 can induce any kind of primary headache. It is thought that the two conditions occur co incidentally.[45] It is thought that the number of reported cases combining both tension-type headache and migraine and Chiari type I malformation is very low and anecdotal.[45, 13]

Sempere et al found 1 case of CM-1 in 580 patients with non acute headache (0.17%).[13] A frequency lower than that reported in otherwise normal adults (1%).[28]

In children with headaches the frequency of CM-1 is reported between 2.9% to 5.8%.[32, 46] As mentioned the frequency of BTE has not been included in these studies.

1.5 Motivation for the study:

The current TE definition is flawed with poor clinicoradiological correlation, as a result there are numerous controversies surrounding TE assessment and management [23] Due to definition there is a paucity of literature on borderline tonsillar ectopia which needs to be included whilst the definition and understanding of hindbrain herniation is evolving.

Headache is the most common presenting symptom in patients with TE (CM-1 + BTE). CMH accounts for only a minority of these headaches. CMH is the only type of headache in CM that

should now be operated, but CMH features may at times be difficult to differentiate from primary headaches. Primary headaches can be debilitating it stands to reason that more patients without clear indications for surgery may be referred to neurologists and pain specialists or detected by neurologists. Even if TE does not play a causative role in headaches it may contribute to sensitization and pain modulation- this needs further exploration.[27]

Although studies in CM-1 patients have found the prevalence of common primary headache disorders to be similar to that of the general population, chronic daily headache and chronic migraine occur with increased frequency. [4,6, 38,39]

More recently, it has been suggested that pain associated with CM 1 should be seen in a wide vision and needs to be managed by a neurologist or pain specialist regardless from surgical indication.[27]

For these reasons we felt that there is a need to quantify the extent of tonsillar ectopia (BTE and CM-1) in primary headache patients.

Objectives:

1. To determine the frequency of cerebellar tonsillar ectopia (both borderline tonsillar ectopia and Chiari 1 malformation) in patients with primary headache disorder
2. To compare the frequency of BTE to that reported in the neuroradiological series by Aitken et al.[5](there is no reported prevalence of BTE in the general population in the literature)
3. To compare the frequency of CM-1 in patients with primary headache to the estimated prevalence of the general population.

Methods

1. Study design:

- A retrospective cross sectional study

2. Study Population:

- Adult patients with primary headache disorders seen at the private practice of Prof G Modi; Life Health Brenthurst clinic, Parktown, Johannesburg
- Inclusion criteria:
    - Patients 18 years of age and older
    - Patients diagnosed with primary headache disorder and MRI Brain scans
    - A non-contributory neurological examination
- Exclusion criteria:
    - Patients with structural abnormalities other than tonsillar ectopia or unrelated to Chiari malformation on MRI (structural abnormalities are those thought to cause mass effect and affect position of cerebellar tonsils, lesions not thought to affect the cerebellar tonsillar position were not excluded e.g. nonspecific white matter lesions – which can be found in patients with migraine)
    - Features of low intracranial pressure on MRI- (pachymeningeal enhancement, small ventricles, pituitary enlargement, subdural effusions and prominence of spinal epidural venous engorgement)
    - Abnormal neurological examination
    - Patients without MRI scans
- Sample size and selection:
    - A convenient sample size of an estimated 1000 patients was initially envisaged but due to time constraints 299 patients were recruited.

(To my knowledge this is the first study of the frequency of tonsillar ectopia in primary headache patients in the South African population, therefore a convenient sampling method was opted for.) The study can act as a pilot study for future more correct estimations of sample size.

A minimum sample size of 74 patients would have been required to detect a 20% difference in proportions where the prevalence of CM-1 in the population is estimated to be 1% (or 0.77%) to get 80% power at 5% level of significance.

The studies second objective could be strengthened by a future study in the South African population of frequency of tonsillar ectopia in a neuroradiological series. Ideally this study's result should be compared to the frequency of tonsillar ectopia in a South African neuroradiological series but as this data is unavailable it will be compared to the global reported frequency.

3. Methods/Techniques:

- Data will be collected using patient's files and clinical records kept at the Life Brenthurst Clinic- practice of Prof G Modi. Patient demographics, type of headache diagnosed and measurement of tonsillar ectopia will be obtained from these files and recorded on data sheets.
- Data will be captured using an excel spreadsheet.
- The MRI at the Life Brenthurst is a Siemens 1 tesla with 1mm slice thickness and a standard protocol: Axial T2 weighted fast spin echo sequences, Axial and sagittal FLAIR T2 weighted fast spin echo sequences, sagittal t1 weighted echo sequence. Axial GRE, DWI and ADC.

- Cerebellar tonsillar position will be determined by; firstly drawing a line from the basion to the opisthion on a midsagittal T1-weighted MR image. A line will then be drawn perpendicular to the basion-opisthion line to extend either superiorly or inferiorly to the tip of the cerebellar tonsils. The length of this second line from the tonsil tip to the basion-opisthion line will be measured and recorded as the tonsil position. A caudal position to the basion-opisthion line will be assigned a positive value, and a position rostral to the basion-opisthion line will be assigned a negative value. Tonsils that end at the basion-opisthion line will be assigned a value of 0. Measurements will be recorded to the nearest millimetre.[24]
- Right , left and midline tonsillar measurements will be taken (sagittal plane)
- The lowest tonsillar position viewed in both coronal and sagittal views will be recorded
- Cerebellar tonsil position will be divided into 3 groups namely :

  Normal: tonsillar ectopia < 3mm below the foramen magnum
  BTE: tonsillar ectopia of 3mm to < 5mm below the foramen magnum
  CM-1: tonsillar ectopia ≥ 5mm below the foramen magnum

4. Variables:

- Variables will be measured as both categories and numbers. Data will be collected with the aid of a data sheet appropriately designed, in consultation with a biostatistician, to fulfil the described objectives (appendix A).

Statistical analysis:

To compute the data analysis, the STATA 13.1 statistical package will be used. To fulfil objective 1 of determining the frequency of tonsillar ectopia in patients with headache. Frequency tables will be computed and proportions test will be used to compare the proportions of patients with tonsillar ectopia versus that of the general population.

Data collected will be analysed in consultation with a biostatistician.

Ethics

Ethics approval will be obtained from the University of Witwatersrand Postgraduate Committee and the Human Research Ethical Committee of the University of Witwatersrand.

Timing

	August	September	October	November	December	January	February	March	April	May	June	July	August	September	October
Protocol development	■	■	■	■	■										
Protocol assessment						■	■								
Ethics application						■	■								
Collecting data								■	■						
Data analysis										■	■	■			
Writing up paper													■	■	■

Figure 4: Gant chart showing the timing of each research component.

Funding

All costs incurred during the undertaking of the study will be paid for personally. No costs will be imposed on the hospital or patients and no extra funding will be obtained.

Study Limitations:

- The retrospective nature of the study may affect its accuracy, relying on the data available in patient's files. Incomplete, missing or inaccurately completed files will affect the quality of data.
- Diagnosis of headache will be according to a Chief specialist neurologist and not according to ICHD-3
- Sampling Bias; our sample consists of patients with primary headaches that are seen by a neurologist and an MRI has been requested/done i.e. it is not a consecutive sample. This may reflect a group of patients with more severe headaches or patients with more red flags, thus the sample is not a true representation of the general headache population
- Sample size will be limited due to time
- Our study could be strengthened if the frequency of BTE is reported in a South African adult neuroradiological series or at our centre.

Study strengths:

- This will be the first study to evaluate the frequency of tonsillar ectopia in primary headache patients in South Africa
- This will be the first study to include frequency of borderline cerebellar tonsillar ectopia in primary headache patients
- The Sampling bias is also a strength as it will evaluate the problem in the population group for which it is intended. The aim is to quantify the problem of tonsillar ectopia in patients with MRIs which may represent more severe cases, it is not necessarily needed in patients that respond well to medication and are easily diagnosed.

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Chapter 2: Proposed Manuscript

Background:

Chronic headaches are common and lead to significant distress and functional impairment.[1] Certain medical conditions are associated with a higher frequency of headaches.[2] Borderline cerebellar tonsillar ectopia (BTE) which may be defined as the downward extension of the cerebellar tonsils <5 mm below the foramen magnum detected on magnetic resonance imaging (MRI) and Chiari type 1 malformation (CM-1) defined as downward extension of cerebellar tonsils ≥ 5mm below the foramen magnum detected on MRI are among these conditions. [2,3] Although questions still persist about the clinical significance of this entity on headache, patients with cerebellar tonsillar ectopia (BTE + CM-1) have a higher frequency of headaches (30-81%) than the general population and severe headaches have been reported in 16% of patients.[2,4,5] Patients with CM-1 and BTE are known to present with a spectrum of headache disorders. Few studies have described the relationship between primary headache disorders and CM-1, even fewer have included BTE. [6]

Headache:

Headache is the most common presenting complaint in general and neurological consultation.[7] Headache can be the presenting feature of serious underlying conditions such as brain tumours i.e. secondary headaches or headache may be benign and due to a primary pain disorder such as migraine and tension type headaches.[7,8] Even though primary headache disorders are considered to be benign they are associated with significant morbidity.[1]

Differentiating primary from secondary headache disorders is still a challenge for most clinicians.[9] The International classification of headache disorders, 3rd edition (ICDH-3) aims to bring uniformity in headache diagnosis and assists clinicians in deciding whether a headache

is primary or secondary.[10] It however remains a useful tool and does not replace the clinical diagnostic process – history, examination and investigations.[7,10,11]

In practice clinicians are aware that patients do not always present in a manner that fulfils the criteria described in ICHD-3 beta. Primary headaches may at times present atypically without ICHD-3 criteria being fulfilled, secondary headaches may mimic primary headaches, or both may coexist. These variations in presentation can make headache diagnosis difficult.[9]

Neuroimaging is a modality used to detect intracranial abnormalities that cause headaches. About 90% of all headaches are primary type headaches where MRI scans of the brain will not reveal any pathology responsible for headaches.[9,12] The rate of significant intracranial abnormalities in patients with headache varies according to the methodology used in different studies.[11] In the study by Sempere et al the rate of significant intracranial abnormalities on CT and MRI in patients with non acute headaches and normal neurological examination was 0.9%.[13]The crude prevalence of incidental findings on brain MRI is 2.7%- 4.7% depending on the resolution of MRI used.[12,14]

With some conditions, such as cerebellar tonsillar ectopia, it may not be possible to say with certainty that the headache is or is not related to the structural lesion.[9] Most neuroimaging series do not include or report on BTE. Furthermore, if not directly investigated for, 57% of patients with tonsillar ectopia will be missed on routine MRI reporting.[15]

It is not uncommon to order neuroimaging for a patient with headache and receive a report of cerebellar tonsillar ectopia. Tonsillar ectopia is similar to brain tumours in that it is a condition that may be managed neurosurgically and they are infrequently detected on neuroimaging but frequently present with isolated headaches.[16]

Although there have been advances in the understanding of cerebellar tonsillar ectopia, questions still persist about the clinical significance of this entity in patients with headache.

Cerebellar Tonsillar Ectopia:

Cerebellar tonsillar ectopia refers to the herniation or descent of the cerebellar tonsils (the paraflocculus) below the foramen magnum.[17,18]

It is a developmental hindbrain abnormality originally described by Hans Chiari in in 1891-1896.[19] Chiari described a spectrum of 4 types of cerebellar ectopy on the post-mortem of children and adolescents.[3,19,20] The type I malformation is the most clinically relevant of the four malformations due to a high mortality occurring early in life in types II-IV. The degree of cerebellar herniation was however not defined.[19]

With the advent and availability of MRI this pathological entity was translated on neuroimaging. It is generally accepted that displacement of one or both cerebellar tonsils 5 mm or more below the basion-opisthion line (foramen magnum) is the basis for the neuroradiological diagnosis of Chiari 1 malformation (CM-1) or a borderline position (3–5 mm below the foramen magnum) should be regarded as pathological when accompanied by other elements of the malformation, like syringohydromyelia and/or cervico-medullary kinking. Without accompanying elements of CM-1 or evidence of posterior fossa crowding, tonsillar ectopia of 3-5mm below the foramen magnum is considered borderline and less than 3mm is considered normal and of no clinical significance. [3,20]

However even with this generally accepted definition heterogeneity still exists in the literature.[21]

Definitions and Clinical Correlates:

Strict adherence to the radiologic definitions are not always useful clinically as patients classified as radiologically normal or borderline may present with classic neurologic signs and symptoms as well as syringomyelia associated with CM-1 that may be amenable to

neurosurgical intervention .[3,17] Furthermore 14-30% of patients with CM-1 are asymptomatic.[5] Thus, the use of a discrete 5-mm boundary for a clinical syndrome is flawed.[15]

There is consensus in the literature that although the current Chiari classification is useful in categorizing patients it may not represent a continuum of the same disease.[19] Our current understanding is based on a dated nonstandardized definition. There is a need to redefine these malformations in order to uncover the natural history of the disease and how symptoms relate to this disorder.[19,22,23] "The radiological criteria for tonsillar herniation are not absolute and should be considered within the clinicopathological context".[16,33]

With newer imaging modalities available, more research is being done to try to understand the significance of cerebellar tonsillar ectopia found on MRI to explain the clinicoradiological mismatch.

Due to current definition most research has ignored BTE or included it in control groups. It is for this reason that our study will include and focus on BTE instead of just CM-1.

Epidemiology:

The estimated prevalence of CM-1 found in neuroradiologic series is 0.5%-3.5% in general, 0.56%- 0.77% on MRI studies and 0.62% in anatomical dissection studies. The exact prevalence in the general population is unknown.[24] Most series have reported slight female predominance (2-3:1).[18,25] The prevalence or frequency of BTE on MRI, to my knowledge has not been reported.[3] However in a study by Aitken et al BTE (2-4 mm) was noted in 19 patients of 5248 MRI scans done, or 0.4% of all the head and spine magnetic resonance imaging performed in the study.[5]

Clinical Presentation:

CM -1 may be asymptomatic or symptoms may be caused by compression of the spinal cord or brainstem or complications of a syrinx.[3,4,18] Headache is however the most common presenting symptom in patients with CM-1 and BTE (30-81%) a frequency greater than the general population. [3,4,5,17,18]

CM-1 typically presents in adolescence or adulthood- even though tonsillar descent decreases with age. The mean age of presentation is 35.9 ± 16.8 yrs. but with availability of MRI it is now commonly diagnosed in children.[15,18] Older age at diagnosis is a predictor for more severe symptoms and headache occurrence.[5]

Management:

Currently patients with CM-1 are managed surgically or conservatively.[20,21]

Recent literature has clarified some indications for surgery in patients with CM-1 and headache. Mild headaches or headaches that are clearly migrainous in origin should be primarily managed medically due to high rate of reported recurrence post surgery.[5,10] Only patients with occipital headaches that fulfil criteria for "Headache attributed to Chiari malformation type 1", ICHD-3(beta) should be treated surgically.[10]

Despite this however the controversy and uncertainty regarding the indications for surgery remains.[26] In a survey of neurosurgeons, only 46% opted to operate if confronted with a patient with occipital headache as the only symptom, in the absence of syringomyelia even though 67-100% of patients with suboccipital headache were reported to benefit from surgery.[5] This statistic reflects uncertainty in that it is almost 50:50. Due to the numerous controversies surrounding TE some centres have found that many patients receive surgical indication without fitting surgical criteria.[26]

In a review of surgical case series by Arnautovic et al it was found that only 1 publication was from Africa and 79% from the United States and Europe.[24,27] With only 1 African publication it is not clear what the South African consensus on the management of Chiari malformation or tonsillar ectopia is, and whether it is any different from internationally accepted practice.[27]

Headache and Tonsillar ectopia:

Patients with CM-1 and BTE experience a spectrum of headache disorders; primary headaches as well a particular type of occipital headache now classified by the ICHD-3 beta as Headache attributed to CM1 (CMH).[26]

Headache attributed to Chiari type 1 malformation (CMH):

CMH is described as being occipital or suboccipital, of short duration (less than 5 minutes) and provoked by cough, exertion or other Valsalva-like manoeuvres. It is the only type of headache in CM patients that now has a surgical indication with careful monitoring advised for other headaches.[10]

CMH is relatively rare in patients with CM-1 accounting for 13.4-28% of CM-1 patients with headache and 5% of BTE patients.[4,5,26,28]

Primary Headache disorders and cerebellar tonsillar ectopia:

Pain in the occipital-suboccipital region or headache that is precipitated by cough or Valsalva manoeuvres suggests symptomatic CM 1,[10] however symptoms of migraine and TTH also include occipital and suboccipital pain and the worsening of headache by cough or other Valsalva-like manoeuvre. These features are present in high percentage of TE patients with headache (87%).[4,5,28] Differentiating CMH from primary headaches in patients with CM-1 can thus be challenging.[29]

In both Toldo's and Pascual's series (45 TE patients and 50 CM-1 patients respectively) the incidence of migraine and tension-type headache was reported to be in accord with that of the general population.[4,28] In Stovner's series of 34 patients with CM-1 although the frequency of migraine was reported to be similar to general population the proportion of continuous daily headache (CDH) (24%) was higher than the expected prevalence of CDH in the general population (4% to 5%, up to 9% in middle-aged women).[30] Kaplan et al also reported the frequency of episodic migraine to be similar to population based studies but found a threefold increase frequency of chronic migraine in CM-1 patients. Patients with CM also presented with more frequent and severe CDH at a younger age than controls. Kaplan et al concluded that CM-1 may play a role in chronic migraine but further study was needed to clarify this hypothesis. [6]

Theoretically there are common structures involved in both primary headache disorders as well as in TE. In the pathophysiology of migraine the cerebellum plays a role in aura (non apparent) and pain modulation, the brainstem also has an important role in pain modulation and sensitization in both TTH and migraine , C1 and c2 mediate pain from the occiput- these structures are also involved in TE.[6]

Newer imaging modalities have shown possible links between the 2 entities.

MRI studies identified changes consistent with iron deposition in the periaqueductal grey (PAG) area in subjects with episodic migraines and CM. Repeated central sensitization or repetitive activation at the level of the PAG, is associated with high iron turnover and permanent neuronal damage. The PAG is a crucial component in the modulation of descending inhibitory pathways.[6]

Diffusion tensor imaging (DTI) is a non-invasive imaging modality that can identify microstructural pathological alterations such as the axonal or myelin damage, and provides a

quantitative assessment of water diffusion in tissues in relation to isotropic and anisotropic diffusion. DTI parameters have shown increased features of microstructural changes in the brainstem of patients BTE and CM-1 when compared to controls.[31]

This may support theories of increased central pain sensitization and poor pain modulation in patients with CM1 and BTE and primary headache disorders.[31]

Summary:

Despite advances in the understanding of Chiari malformations, the evaluation and treatment of headache related to CM-1 is still difficult.[29]

The current view is that TE and primary headaches occur co incidentally.[4,28] However this view is based on few studies with small numbers of patients and supports a non neurosurgical approach to the treatment of TE. This is supported by recurrence of frontal headache in patients treated surgically.[10,32] The current view although correctly advocating against neurosurgical intervention does not adequately explain why headaches are the most common presenting complaint in TE.

Recent studies have suggested pain associated with CM 1 should be seen in a wide vision and needs to be managed by a neurologist or pain specialist regardless of surgical indication.[26]

Furthermore the definition and understanding of TE is evolving. We aim to provide an important piece of unreported information i.e. the frequency of BTE in primary headache disorders to assist future research in understanding the relationship between the two disorders.

Sempere et al found 1 case of CM-1 in 580 patients that had MRI brain scans for non-acute headache (0.17%).[13] A frequency lower than that reported in otherwise normal adults (1%).[24]

In children with headaches the frequency of CM-1 is reported between 2.9% to 5.8%.[29, 33] As mentioned the frequency of BTE has not been included in these studies.

Smith et al showed that, of the patients with tonsils 5 mm or more below the foramen magnum, CM was mentioned in the radiology report of only 39 (53%) of 74 patients, therefore unless directly investigated for 53% of patients with CM-1 will be missed on routine MRI reporting[15], thus the extent of the problem of cerebellar tonsillar ectopia has not been adequately quantified in the headache population to date.

Aim:

1. To determine the frequency of cerebellar tonsillar ectopia (both borderline tonsillar ectopia and CM-1) in patients with primary headache disorder
2. To compare the frequency of CM-1 in patients with primary headache to the estimated frequency of the general population. To compare the frequency of BTE to that reported in the neuroradiological series by Aitken et al (there is no reported prevalence of BTE in the general population in the literature)

Methods:

From a database of MRI brain scans done in 2004 a total of 342 scans were found. All MRI brain scans were done using a Siemen's 1 Tesla with 1mm slice thickness. Of the 342 scans, 16 patients were excluded due to age alone (<18years) and 27 patients were excluded due to an abnormal finding on MRI.

The MRI brain scans and files of the remaining 299 adult patients diagnosed with primary headache disorder at the private practice of senior neurologist Prof G Modi at the Life Brenthurst Clinic in Parktown Johannesburg were retrospectively reviewed. Cerebellar tonsillar position was measured in relation to the foramen magnum and the frequency of the lowest cerebellar tonsillar position is reported. Eligible patients included adults aged 18 and older with primary headache disorders, a non-contributory neurological exam and MRI brain scans. Patients were excluded if neuroimaging or clinical examination suggested a secondary

cause of headache or secondary cause of tonsillar ectopia i.e. raised or low intracranial pressure. The study was approved by the University of Witwatersrand Human Research Ethics Committee (clearance number – M170369).

Study definitions and measures:

- Tonsil position was determined firstly drawing a line from the basion to the opisthion on a midsagittal T1-weighted MR image. A line was then drawn perpendicular to the basion-opisthion line to extend either superiorly or inferiorly to the tip of the cerebellar tonsils. The length of this second line from the tonsil tip to the basion-opisthion line was measured and recorded as the tonsil position. A caudal position to the basion-opisthion line was assigned a positive value, and a position rostral to the basion-opisthion line was assigned a negative value. Tonsils that ended at the basion-opisthion line was assigned a value of 0. Measurements were recorded to the nearest millimetre.[34]
- Right , left and midline tonsillar measurements were taken (sagittal plane)
- The lowest tonsillar position viewed in sagittal views were recorded
- Cerebellar tonsil position was divided into 3 groups namely :

  Normal: tonsillar ectopia < 3mm below the foramen magnum
  BTE: tonsillar ectopia of 3mm to < 5mm below the foramen magnum
  CM-1: tonsillar ectopia ≥ 5mm below the foramen magnum

Statistical Analysis:

- Frequency tables were computed using STATA 13.1 statistical package to determine the frequencies of normal, BTE, CM-1 in the sample.
- Proportions tests were used to compare the proportions of patients with BTE and CM-1 to that of the general population. ($p < 0.05$ = significant)

- Fischer's exact test was used to compare the significance of lower tonsillar position according to ethnicity, diagnosis and gender.

Results:

Patient Demographics and Diagnosis:

There were 299 adult patients with primary headache disorders and MRI brain scans. Patients aged between 18 and 87yrs with a mean age of 40.1yrs (SD 13.5yrs) and a median age of 40yrs. 66.2% (n=198) were female and 33.8% (n=101) were male. 49.5% (n=148) were black, 24.4% (n= 73) white, 20.4% (n=61) Asian and 5.7% (n=17) coloured. 84.9% were diagnosed with migraine and 15.1% with tension type headache.

Table 1: Patient Demographics

Patient Demographics			
Characteristics		Total	
		N	%
Sex	FEMALE	198	66.2%
	MALE	101	33.8%
Ethnicity	BLACK	148	49.5%
	COLOURED	17	5.7%
	ASIAN	61	20.4%
	WHITE	73	24.4%
Diagnosis	MIGRAINE	254	84.9%
	TTH	45	15.1%
	Total	**299**	**100**

Cerebellar tonsillar position:

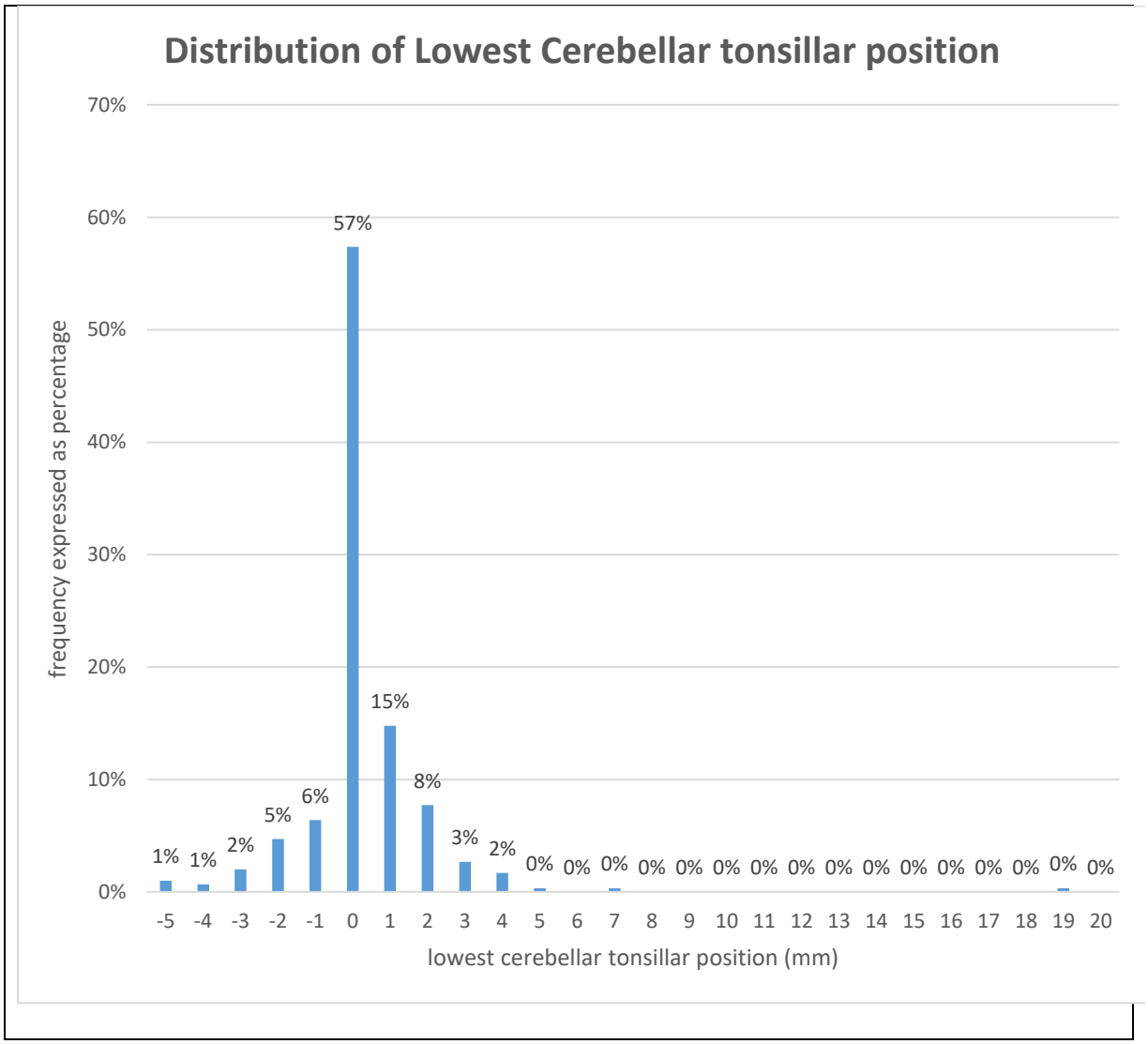


Figure 1: Histogram of the distribution of lowest tonsillar position according to frequency

(0 represents the foramen magnum. Negative numbers represent a position rostral to the foramen magnum and positive numbers represent a position caudal to the foramen magnum i.e. cerebellar tonsillar ectopia.)

Table 2: Summary of Histogram statistics

Total number of patients (n)	**299**
Mean Lowest tonsillar position (mm)	0.3
Standard deviation of lowest tonsillar position	1.8
Median lowest tonsillar position	0
Skewness	3.9
Range	24
Highest lowest tonsillar position (min)	-5
Lowest tonsillar position (max)	19

In 299 patients with primary headache disorder the cerebellar tonsillar position ranged from 5mm (-5mm) above the foramen magnum to 19mm below (+19mm). The mean tonsillar position was 0.3mm (below the level of the foramen magnum) and the median was 0mm (at the level of the foramen magnum).

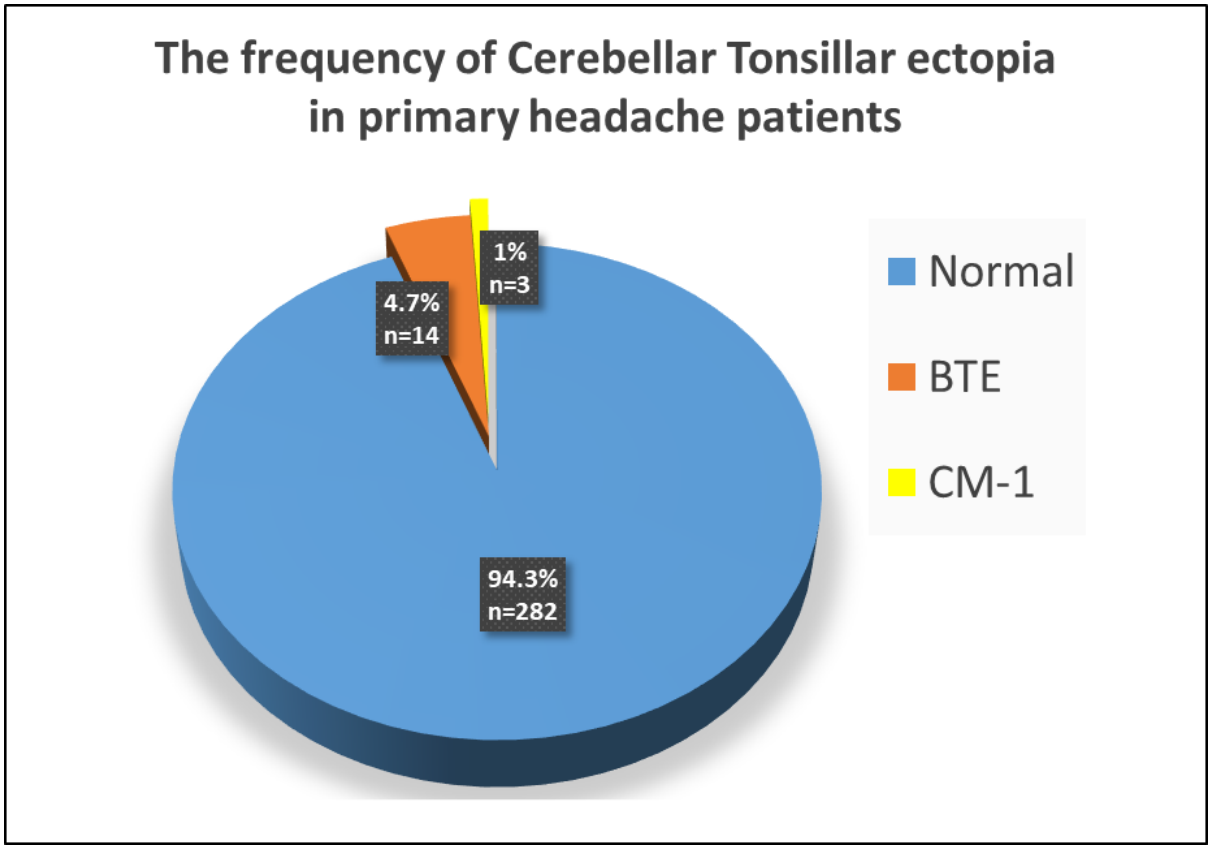


Figure 2: Pie chart of the frequency of cerebellar tonsillar ectopia in primary headache patients

Of the 299 patients with primary headache disorder 14 had BTE (4.7%) and 3 CM-1 (1%), with 282 (94.3%) of patients falling into the normal category. Of the 3 patients with CM-1, 1 patient had associated basilar invagination.

Table 3: Lowest Cerebellar tonsillar position and Gender, Ethnicity and Diagnosis:

Characteristics		Lowest tonsillar position category								
		Normal		BTE		CM-1		Total		Fisher' Exact test P-value
		n (282)	%	N (14)	%	N (3)	%	N (299)	%	
Sex	FEMALE	185	93.4	11	5.6	2	1.0	198	100	**0.73**
	MALE	97	96.0	3	3.0	1	1.0	101	100	
Ethnicity	BLACK	139	93.9	6	4.1	3	2.0	148	100	**0.574**
	COLOURED	15	88.2	2	11.8	0	0.0	17	100	
	INDIAN	58	95.1	3	4.9	0	0.0	61	100	
	WHITE	70	95.9	3	4.1	0	0.0	73	100	
Diagnosis	MIGRAINE	238	93.7	13	5.1	3	1.2	254	100	**0.818**
	TTH	44	97.8	1	2.2	0	0	45	100	
	Total	**282**	**94.3**	**14**	**4.7**	**3**	**1**	**299**	**100**	

There is no significant association or correlation between Lowest tonsillar position and sex, ethnicity, or diagnosis (P>0.005).

Table 4: Age and Cerebellar Tonsillar position:

Age category (years)	Normal		BTE		CM-1		Total	
	n	%	n	%	n	%	n	%
18-29	63	22.3	4	28.6	0	0.0	67	22.4
30-39	74	26.2	2	14.3	2	66.7	78	26.1
40-49	82	29.1	5	35.7	1	33.3	88	29.4
50-59	42	14.9	2	14.3	0	0.0	44	14.7
70+	21	7.5	1	7.1	0	0.0	22	7.4
Total	282	100	14	100	3	100	299	100

The three patients with CM-1 were aged 34, 38 and 43.

Table 5: Age and Cerebellar tonsillar position with CM-1 removed:

Age category (years)	Normal		BTE		Total		Lowest tonsil position mean	
	n	%	n	%	n	%	Mean	SD
18-29	63	22.3	4	28.6	67	22.4	0.36	0.07
30-39	74	26.2	2	14.3	78	26.1	0.12	0.11
40-49	82	29.1	5	35.7	88	29.4	0.52	0.27
50-59	42	14.9	2	14.3	44	14.7	-0.18	0.11
70+	21	7.5	1	7.1	22	7.4	0.41	0.62
Total	282	100	14	100	299	100	0.27	0.34

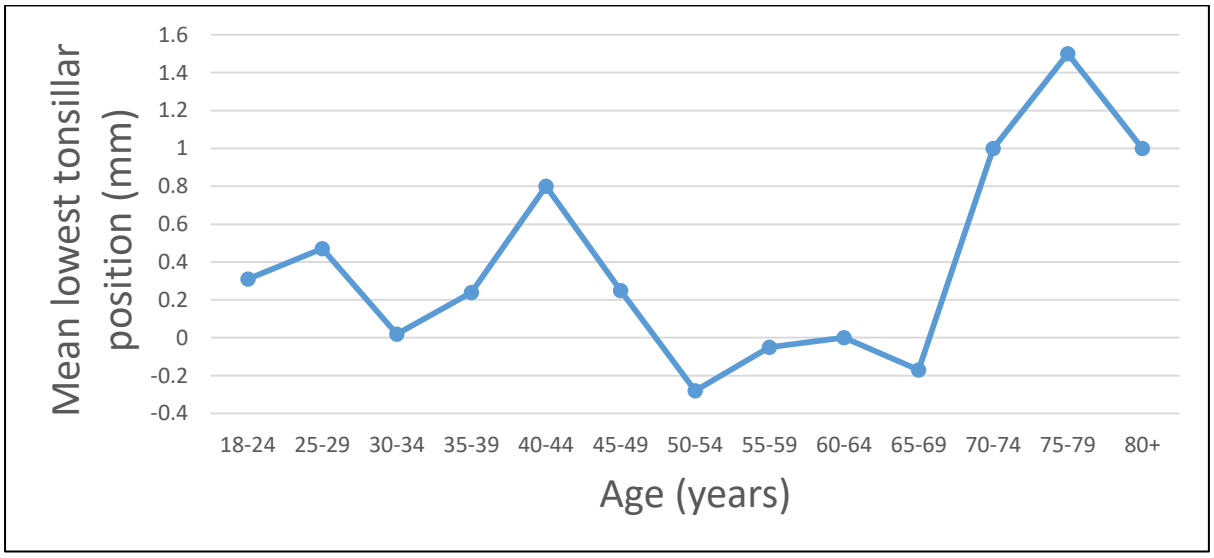
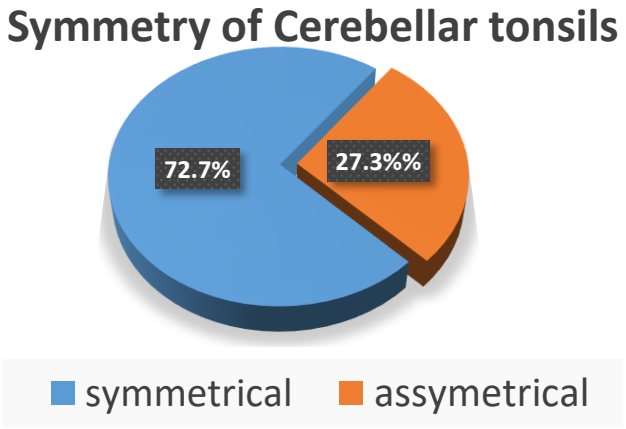


Figure 3: Distribution of lowest tonsillar position by age with CM-1 removed

There was no correlation between tonsillar position and age. However the mean tonsillar position lies below the foramen magnum (positive value) in this primary headache population in most age groups bar ages 50-59.

Symmetry of Cerebellar tonsils:



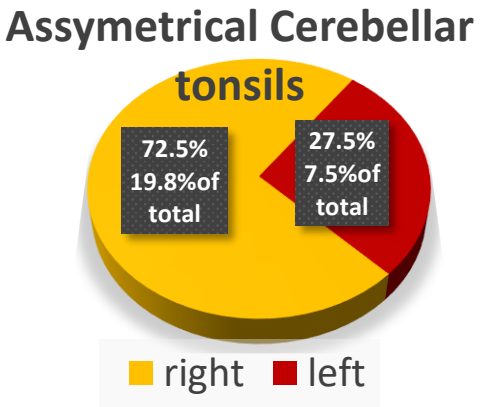


Figure 4: Symmetry of cerebellar tonsillar position

Discussion:

Of the 342 MRI brain scans ordered for patients with headache in 2004, 27 patients (8%) were excluded due to an intracranial abnormality, 315 (92%) patients had normal MRI brain scans. This is in keeping with current literature that reports that approximately 90% of headaches seen in practice are of the primary variety, and less than 10% are of the secondary variety.[11] Of note is that of the 35 patients excluded from this study with intracranial pathology most patients also had an abnormal neurological examination. This is also in keeping with the literature that states

that abnormal neurological examination is a positive predictor for detecting abnormalities on neuroimaging.[13]

Of the 299 adult patients diagnosed with primary headache disorder, 33.8% were male and 66.2% were female, the male female ratio in our sample is 1:2. This reflects that primary headache disorders are more common in women than men and is in keeping with the current literature which reports the male: female ratio for migraine among adults is 1:2 to 1:3, and for TTH is 4:5.[1] In our sample the male female ratio is closer to that of that reported for migraine as migraine was the primary diagnosis in the majority of patients.

The prevalence of headache generally decreases with age.[1] The prevalence of TTH peaks between the ages of 30 and 39 years and the prevalence of migraine increases with age until a peak is reached during the fourth decade of life. The most common age of onset of migraine is in the second and third decades of life.[1] The average age of onset of TTH is higher than for migraine, namely between 25 and 30 years in cross-sectional epidemiological studies.[1] The mean age of our population group was 40, this represents 2 phenomenon i.e. the prevalence of primary headache disorders are more common in those aged 30-39 and that there is a greater tendency for MRI to be ordered in those over the typical age of primary headache onset namely 20-30years.

In our sample 84.9% of patients were diagnosed with migraine and 15 % were diagnosed with tension type headache. This suggests and is in keeping with current view; that although tension type headache is more prevalent, migraine is more severe and more migraneurs may seek specialist care.[1]

Of the 299 patients with primary headache disorder 14 had BTE (4.7%) and 3 CM-1 (1%), with 282 (94.3%) of patients falling into the normal category. Of the 3 patients with CM-1, 1 patient had associated basilar invagination.

A two sample test of proportions comparing the frequency of BTE in our sample (4.7%) to that of the neuroradiological series by Aitken et al (0.4%) showed a difference of 43%, CI 95% 0.0503 to 2.0526, Chi- squared 8.283,Significance level p=0.0040 (significant <0.05). The frequency of BTE in Aitken's neuroradiological series was used as there is no reported prevalence of BTE elsewhere in the literature. Using this reported frequency is not ideal as in Aitkens study BTE was defined as tonsillar ectopia 2-4mm below the foramen magnum and the study population consisted of children.[5]

There were only 3 cases of CM-1 in the study population (1%). A one-sample proportion test comparing the 1% to the hypothesized proportion of CM-1 reported in the "normal population" (0.56%-0.77%)[24], has shown no significant difference between them (p>0.05).

In our series we showed no correlation between age and tonsillar position. However in Milukulis series of a similar 220 patients the patient's ages ranged from (age range 5 months–89 years).[15] The age range in this series 18-87 years perhaps misses the peaks in tonsillar position, or it could be that in headache patients this curve is disrupted. Furthermore the mean tonsillar position in most age groups was below the foramen magnum.

With regard to the symmetry of the cerebellar tonsils. Cerebellar tonsils were symmetrical in 72.7% of patients. In the study by Smith et al tonsillar symmetry was reported to be 84%. In patients with asymmetrical cerebellar tonsils the right (72.5%, 19.8% of total) as in the Smith study was the lower tonsil.[15] We did not show an increase in asymmetry with lower tonsillar position. The significance of this finding is unknown.

Limitations

- This study has several limitations. Our sample of patients is from a single private practice in South Africa.
- Sampling Bias ; our sample consists of patients with primary headaches that are seen by a neurologist and an MRI has been requested/done i.e. it is not a consecutive sample. It may reflect a group of patients with more severe headaches or patients with more red flags, thus the sample is not a true representation of the general headache population
- The Sampling bias is also a strength as it will evaluate the problem in the population group for which it is intended. The aim is to quantify the problem of tonsillar ectopia in patients with MRIs which may represent more severe cases, it is not necessarily needed in patients that respond well to medication and are easily diagnosed.
- We compared the frequencies of BTE to that reported in a neuroradiological series of 1 published study, our study could be strengthened if the frequency of BTE is reported in a South African adult neuroradiological series.
- We could not calculate the true prevalence of BTE or CM-1 in our population as the population our single practice serves is unknown

Conclusion:

Our understanding of cerebellar tonsillar ectopia is constantly evolving. There has been a call for the redefinition of Chiari malformations as it is thought to be an oversimplification of a diverse abnormality with poor clinicoradiological correlation. Whilst some questions have been answered regarding CM-1 most importantly indications for surgery and the CMH as defined in the ICHD-3 beta this has not yet been fully translated into practice. Furthermore the CMH is uncommon.

Headache is the most common symptom in patients with tonsillar ectopia. Although studies in children have shown that the frequency of primary headache disorders is similar to the general population, more research using new neuroimaging techniques has shown a possible relationship between pain processing pathways involved in the pathogenesis of primary headache disorders and cerebellar tonsillar ectopia . We aim to provide an important piece of information i.e. the frequency of BTE in primary headache disorders which is 4.7%. This percentage is low to advocate investigating patients with primary headache disorders for BTE. However with no indication for surgery these patients may be found by and referred to neurologists and pain specialists, we recommend that follow of this group of patients is needed to determine whether they respond to conventional primary headache treatment algorithms.

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Chapter 3: Appendix

I. Data collection sheet

Demographics:	
Age	
Sex	
Race	
Diagnosed headache type	
Tonsillar position (- mm above foramen magnum, + mm below foramen magnum)	

II. Ethic's clearance certificate

R14/49 Dr Saiesha Dindayal

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170369

NAME: (Principal Investigator)	Dr Saiesha Dindayal
DEPARTMENT:	Neurology Life Brenthurst Clinic - Prof G Modi's Private Practice
PROJECT TITLE:	The Frequency of Cerebellar Tonsillar Ectopia in Primary Headache Patients
DATE CONSIDERED:	31/03/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Girish Modi
APPROVED BY:	Prof P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/04/2017

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 in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized 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 the application 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 March and will therefore be due in the month of March each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

iii. Plagiarism report

The plagiarism software Turn it in was used to review this dissertation. A similarity index of 27% was reported. This relates to the use of standardised definitions, ICDH-3 criteria as well as definitions used in other studies; furthermore, all other similarities have been appropriately referenced.