HEADACHES AS A SYMPTOM IN EPILEPSY

AN INSTITUTION BASED OBSERVATIONAL STUDY

A RESEARCH ARTICLE SUBMITTED TO THE UNIVERSITY OF THE WITWATERSRAND FOR THE PURPOSE OF THE DEGREE OF MASTER OF MEDICINE, NEUROLOGY.

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Declaration

I, Catherine Dendere, declare that this research report is my own work. I am submitting it to the University of the Witwatersrand. It has not been previously submitted for any degree or other purpose at this or any other university.

Signature: .....

Date: 26/11/2018

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I Dr Catherine Dendere ,, as a postgraduate student registered for a MMed at the University of the Witwatersrand declare the following:

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Date 26/11/2018

HEADACHE AS A SYMPTOM IN EPILEPSY

Catherine Dendere and Girish Modi

Abstract

Introduction

Seizure associated headaches have been reported to occur frequently in epileptic patients, resulting in additional disease burden for these patients. However investigations of the characteristics of seizure-associated headaches are rare.

Aim

The purpose of the study is to characterise headaches as a symptom/feature in patients known with epilepsy.

Method

Over a period of six months, 200 patients suffering from epilepsy were recruited from our tertiary epilepsy outpatient clinics. They participated by answering questions from a semi-structured questionnaire regarding their seizure profile, and whether or not they had headaches. The features and characteristics of the patient's seizures and headaches were analysed.

Results

Of the epileptic patients, 45.5% n=91 had seizure associated headaches. No association was found with ethnicity (p=0.181) and employment status (p=0.431). Analysis of the total number of patients that had seizure associated headaches indicated that they comprised of; migraine like 46.1% (n=42), chronic tension type like headache (CTTH) 44% (n=40), and 9.9% (n=9) were unclassified. The most common peri-ictal headache, was post-ictal (occurring only after a seizure) 32.5% (n=65), with migraine like headaches accounting for 16.5% (n=33) followed by tension type headaches with 13.5% (n=27). Headache intensity was reported as severe in 53.8% of all seizure associated headaches.

Conclusion

Seizure associated headaches occur commonly in epileptic patients. They are either migrainous or tension type like in character, of moderate to severe intensity and lasting between 4-to-24 hours. Temporal relation to seizures is usually postictal. This therefore adds to the burden of symptomatology and morbidity in epileptic patients, so we recommend that Physicians managing epileptic patients specifically inquire about and manage epilepsy associated headaches.

Acknowledgements

I would like to thank the Division of Neurology for all the support during this process, and to all those who participated in the study.

CONTENTS

1. RESEARCH PROTOCOL WITH EXPANDED LITERATURE REVIEW

Headaches as a symptom in epilepsy

Introduction and literature review

The assessment of headaches a symptom of epilepsy is often neglected. This is because other symptoms such as disturbance in consciousness or motor phenomenon predominate. [I] Specific epilepsy syndromes have been associated with migraines, including benign rolandic epilepsy and benign occipital epilepsy of childhood. Comorbidity with other primary headache is poorly understood. [2] Headache may be associated with seizures as a preictal, ictal, or postictal phenomenon. Although rare, headaches can also be the sole or predominant clinical manifestation of epileptic seizures. [3] The purpose of his study is to analyse primary headaches as a symptom/feature of epileptic seizures. International Classification of Headache Disorders, Second Edition (ICHD-2) [4] covers the relationship between headaches and epilepsy, where migraine-triggered seizure, "hemicranias epileptic," and postictal headaches are defined. The relationship between headaches and seizures is a complicated one because they are related in numerous ways. A number of anticonvulsants namely (valproate, topiramate, gabapentin) have shown efficacy in migraine prophylaxis. [5]

Headaches are often ignored as a symptom of epileptic seizures. Using a prospective study (Leniger,T et al) [I] analysed the characteristics, frequency, and classification of seizure associated headaches according to the criteria of the International Headache Society (IHS). Over 15 months between March 1, 1999, and August 15, 2000 patients in their respective epilepsy outpatient clinics were interviewed. This was done by using a questionnaire to determine whether their headaches and epileptic seizures occurred independently or in close relation to each other.

They evaluated 341 patients for seizure associated headaches. All patients evaluated had an established diagnosis of epilepsy according to the International League against Epilepsy (ILAE) classification of Epilepsy and Epileptic Syndromes. They defined seizure headache (SH) as a headache beginning an hour before or after the seizure, or both. Headache occurring only before a seizure as Pre-ictal (SH). Peri-ictal (SH), as a headache before, during, and after the seizure; and postictal (SH); as a headache occurring solely after the seizure. The classification of headache type was done based on the criteria of the (IHS).

A visual analogue scale (VAS), where (0, no pain; 10, strongest pain) was used to determine the pain intensity experienced by the patients. According to the ILAE criteria, the individual patient's epilepsy syndromes were classified as generalized or focal.

Of the 341 epilepsy patients recruited, 34% (115) experienced seizure associated headaches. Headaches were always associated with seizure in 60% of the 115 patients. Pre-ictal headaches occurred in 3% of the 115 patients, peri-ictal headaches 27% and 70% of the 115 patients had postictal headaches. Migraine headaches accounted for 55.7% of the 115 whereas 36.5% had tension type headache. There was no relation between seizure headache type and a particular epilepsy syndrome, gender, or family history of migraine. However a background of migraine headache in patients significantly increased the likelihood of developing migraine-like seizure associated headache. They concluded that SH is a common and severe feature in epileptic seizures.

Similar outcomes were established in other studies. (Forderreuther Et al). [6] Investigated the occurrence and symptoms of seizure-associated headaches and the therapeutic interventions used. They analysed one hundred and ten epileptic patients from an epilepsy outpatient centre and a further 15 patients known with postictal headaches were enrolled. Patients partook in a semi-structured consultation about headaches associated with epileptic seizures. They found forty-three patients that only had postictal headaches, one patient had exclusively pre-ictal headaches, three patients were found to have both pre- and postictal headaches. The postictal headaches lasted longer than 4 hours in 62.5% of the patients. For the majority of patients, postictal headaches occurred in more than 50% of the seizures. Recommendations suggested after their study regarding patients with epilepsy and headache comorbidity, that management must address both the epilepsy seizure disorder type and the general guidelines for treating primary headaches. They also concluded that the pathophysiology of seizure associated headaches couldn't be explained by the epileptic syndrome.

Studies on the correlation between epilepsy and headaches are challenging to perform as tension- type headaches (TTHs) occur frequently in the general population, whereas cluster headaches are uncommon. The result of this has been that most studies analyzing the occurrence of headache in patients with epilepsy focus principally on migraine and the results are still contentious.

G Mainieri, et al. [7] recruited 388 patients from tertiary Epilepsy Centres. Their aim was to evaluate the prevalence and symptoms of inter-ictal (inter-IH) and peri-ictal headache (peri-IH) in patients with epilepsy using a semi-structured interview.

Patients aged 17 years participated by completing a self-report form. Patients that were excluded from the study were: patients who reported a lifetime presence of headache; those that had never suffered from headaches; patients who had only been consulted once as a first visit, and proved not to be epileptic or those that had a doubtful diagnosis of epilepsy, patients who had only a single seizure, and those with severe mental retardation.

Physicians performed interviews in patients that had headache. The interviews were semi-standardized and the type of inter-IH and peri-IH, if present, was described. The diagnosis was validated by headache experts according to ICHD-II criteria. Expert epileptologists classified epileptic seizures and syndromes according to the 2010 International League against Epilepsy (ILAE) Commission report.

Their conclusion was that migraine was the most represented type of headache disorder in epileptic patients. Out of 388 enrolled patients 48.5 % had inter-IH and peri-IH was observed in 23.7%. In addition to this post-ictal headache was found to be the most frequent type of peri-IH, occurring in 19 % of patients: 37/74 patients reported a migraine type, 30/74 a TTH, and in seven cases the quality of headache was unclassified. Post-ictal headache (post-IH) was considerably associated with both migraineur and TTH patients. It was also found that post- IH was significantly associated with antiepileptic polytherapy ($P<0.001$), high seizure frequency ($P = 0.002$) and tonic- clonic seizures ($P = 0.043$). [7]

Other research studies have suggested that there is no association between headaches and epilepsy, with conflicting results. Tonini MC et al. [2] assessed the prevalence and features of epilepsy and headache comorbidity amongst patients from nine headache and eleven epilepsy centres of Northern and Central Italy. This multicentred cross-sectional study was conducted between September 2005 and June 2007. The research hypothesis concluded that, if there is an association between epilepsy and headache, the prevalence of comorbidity among patients with either disorder would be expected to be higher than in the general population. [2]It was found that the prevalence of comorbidity in patients with epilepsy and in those with headache overlapped that of the general population. This suggests that there is no association between the two conditions.

Fernando (TG, et al) [8] found the opposite to be true. They did a cross-sectional study from epilepsy outpatient centres to analyse the presence of headaches and their relationship with epileptic seizures. Of the 304 epileptic patients evaluated it was found that frequent seizures were associated with a greater tendency of occurrence of headaches. Headaches occurred in 66.1% of the cases. The highest occurrence was of migraine (32.9% of the patients), followed by tension-type headaches (9.2%). This concluded that there is a high prevalence of headaches in patients with epilepsy.

The nature of the association between headaches and epilepsy is unclear. A number of possible explanations exist; the two coexist by chance; headache is part of seizures or post-ictal state; both have a common underlying aetiology; and that epilepsy mimics the symptoms of migraine.

The hypothesis that migraine and epilepsy are related dates back to the 19th century. Both disorders are characterized by transient paroxysmal episodes of altered brain function with pathophysiological, clinical and therapeutic overlap. [5] Andermann's, observed that migraine and epilepsy at times occurred in the same individual. This has been interpreted in three ways: Firstly, migraine and epilepsy are both relatively common in the general population and therefore, occur together in some people. Secondly, migraine and epilepsy may share a pathophysiologic or genetic basis, which would explain their occasional coexistence. [5]

In their paper (Papetti, L et al) [5] the relationship between migraine and epilepsy in terms of epidemiology and pathophysiology in regard to translational research, clinical correlations and classifications. They showed that seizures and headaches share pathophysiological mechanisms. These especially involve neurotransmitters and ion channel dysfunctions. It has also been shown that photosensitivity seems to play a role in the connection.

(Dana Ekstein, et al) [9] Reviewed data from clinical reports. According to the data presented in their review, post-IH is prevalent, clinically significant, and frequently reveals migraine characteristics. People at the highest risk of having post-IH are young adults, both women and men, with relatively severe and longstanding epilepsy. Additional risk factors include patients that have generalized tonic-clonic seizures GTCSs and a personal history of inter- IHs. An occipital epileptogenic focus has also been found to be a possible additional risk factor. The high risk of having post-IH, especially after GTCSs, might help differentiate epileptic from clinically similar non-epileptic psychogenic spells.

Particularly when taken together with fatigue. It has been suggested that laterality of post-IH may correlate with the location of the epileptogenic focus in patients with focal epilepsy. However there is not enough evidence to support the use of this association in clinical practice. [9]

Post-IHs occur more commonly in generalised epilepsy as migraine headaches, with inter-IR as a specific risk factor. Post-IH are underdiagnosed and undertreated, leading to patients self-medicating. (Stephanus Schmidt Botha,l et al) [10] Described the clinical characteristics of post-IH in patients with generalised epilepsy in a tertiary hospital outpatient clinic. They also evaluated potential associations between post-IHs and demographics, seizure type, family history and medication usage.

An observational, cross-sectional design study was conducted. Two hundred patients with generalised epilepsy were recruited from the neurology clinic at the Steve Biko Academic Hospital, a tertiary care facility in Pretoria, South Africa. Based on the presence or absence of post-IHs the patients were divided into the study and control groups. Patients from 18 years or older, meeting the criteria for generalised epilepsy according to the (ILEA) were enrolled into the study.

Patients participated in a semi-structured interview. Data collected included information regarding demographics, seizure and headache characteristics, medication usage, and localisation and accompanying symptoms. Patients indicated when they had self-medicated for post-IHs or whether a doctor had prescribed their medication.

The study confirmed that post-IHs in patients with generalised epilepsy was a common occurrence. From the total of two hundred recruited patients with generalized epilepsy, 52% (104) were found to have post-IHs. Among the subjects with post-IHs, the majority, 63% reported experiencing headache after every seizure, with severe headache lasting up to 24 hours. Majority of patients' headaches (60%) could be classified as either migraine or probable migraine indicating an association between generalised seizures and migraine post-IHs headache. No significant associations with the type of seizures, age or race and the post-IH type was found.

Inter-IHs, and in particular migraine, is widely accepted to present a relevant co-morbidity of epilepsy. The prevalence rates are believed to be higher in patients with epilepsy than in the general population. However, the assumption of co-morbidity is mainly based on a single study that reported a 2.4-fold increased risk of migraine in a cohort of almost 2000 patients with epilepsy compared with their relatives without epilepsy. More recent studies presented conflicting results, with migraine prevalence rates in patients with epilepsy higher or lower than or equal to the general figures in adults. This ranges from 11% to 15%. Peri-IHs has been described retrospectively to occur in 28-47% of adult patients. They are commonly of migrainous or tension-type headache-like character.

(Duchaczek B, et al) [11] Recruited patients (2: 18 years) with epilepsy or unprovoked seizures

attending their tertiary epilepsy outpatient clinic. The patients underwent a semi-structured interview regarding occurrence and characteristics of inter and peri-IHs. Clinical variables in patients with and without inter and peri-IHs and seizure types were then compared.

The aim of the study was to address the concept of co-morbidity of epilepsy and inter-IH/migraine epidemiologically. In addition to this frequency, clinical characteristics and treatment of peri-IHs in those patients was analyzed with an emphasis on potential predictors of peri-IHs as a complication of seizures. Out of 201 patients, 56.2% reported headache, inter-IHs occurred in 34.3% and 10.9% suffered from migraine. Peri-IHs was reported by 35.3%, occurring as pre-IHs in 16 and as post-IHs in 61 cases. Peri-IH character was migrainous in 26.8% and TTH-like in 62%, the mean severity was 6.1 ± 2.2 cm. The peri-IHs were treated in less than 40% of patients, only 11% sought specific medical advice. Predictors were low age at epilepsy onset ($P < 0.0001$), antiepileptic drug polytherapy ($P = 0.036$) and GTCs ($P < 0.0001$).

They concluded the following: In patients with epilepsy, inter-IHs, and particularly migraines, are less common than expected, challenging the widely held concept of co-morbidity of the two conditions; Peri-IH are frequent, severe and undertreated which results in an additional burden to seizures. [11]

AIM OF STUDY

The aim of the study will be to analyse primary headaches as a symptom/feature of epileptic seizures and to determine the kind of association that exists between the different kinds of primary headaches and epilepsy syndromes for patients who attend the Chris Hani Baragwaneth Hospital and the Charlotte Max.eke Johannesburg Academic Hospital outpatient clinics. The description will include demographic information, headache type and epilepsy syndromes. The association between the two disorders will be classified and categorized with the aim of determining whether or not a correlation between the two disorders exits, and if so to describe it.

METHOD

A questionnaire based, observational, descriptive study will be conducted over a period of six consecutive calendar months. Patients will be interviewed, in conjunction with supporting information that will be obtained from their clinical records, during the scheduled epilepsy outpatient department appointments.

Patients will be interviewed using a five-part questionnaire. The first part of the questionnaire will assess demographic data, which will include age, gender, ethnicity and employment status (appendix 1). The second part of the questionnaire will assess the type of epilepsy syndrome (appendix 2), classifying them as either generalised or partial according to the International League Against Epilepsy (I.L.A.E.) Classification [12] In the subgroup of epileptic patients with headaches, EEG and brain CT scan results will be recorded. The third section of the questionnaire will assess the headache subtype (appendix 3). The fourth and fifth parts of the questionnaire will assess the presence of comorbidities in the presence of the various headache and epilepsy syndrome subtypes respectively (appendix 4 and 5). Inclusion criteria will include a confirmed diagnosis of epilepsy according to the I.L.A.E. Classification [12], as well as patients being of adult age (>18 years). Patients will be excluded from the study if they presented with provoked seizures (i.e. patients with seizures secondary to metabolic derangements, toxins or other reversible triggers). Patients with a history of head injuries and patients that have been diagnosed with secondary headache will also be excluded

The study will be conducted at the Chris Hani Baragwaneth Hospital, and the Charlotte Maxeke Johannesburg Academic hospital, at the respective epilepsy outpatient clinics. Written informed consent will be obtained from each participant. All patients will be counselled as to the purpose of the study, confidentiality of medical information, and the right to refuse participation.

The statistical analysis data will be captured in Microsoft Excel and exported into SPSS. A pvalue of 0.05, or less, will be used to indicate statistical significance. Statistical analysis will be performed using means, analysis of variance and Chi-squared analysis appropriate to determine if associations existed between any of the variables associated with patient's seizures, demographics and headache subtypes. Analysis of association of headaches and seizure control will be included.

Timin2

	Jan	Feb	Mar	April	May	Jun	July	Aug	Sept	Oct	Nov	Dec
Literature review	X	X										
Preparing protocol	X	X										
Protocol assessment			X									
Ethics application				X								
Collection of data					X	X	X	X	X	X		
Data analysis											X	X
Writing up-paper											X	X

2. Appendices

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2. Appendices

INFORMED CONSENT FORM:

Title of Study: Headaches as a symptom in epilepsy

I confirm that I have been informed by Dr Dendere about the nature of the study. I have also read/it was read to me and I understood the information sheet and have had the opportunity to ask questions.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

I understand that sections of any of my medical records may be looked at by Dr Dendere and authorized parties (Prof G Modi). I am aware that I will not undergo any tests other than routine tests required for my condition however I will be asked questions relating to my condition. Information will be listed on a datasheet and will be anonymously processed into a computerised system. Data will be kept for two years if published or six years if not published, after this period the data will be destroyed. Should you wish to contact us at any stage regarding consent, contact Dr Dendere at 0846706579 or email Catherine.zyambo@yahoo.com or Prof G Modi at 0114884432 or email gmodi@mweb.co.za

I agree to take part in the above mentioned study. I hereby give consent for my records to be used as per the above mentioned conditions and for the purposes of research.

_____

Name and Surname Signature/Mark or Thumbprint Date:

Printed name Signature Date:

Witness (If applicable):

Printed name: Signature: Date:

INFORMATION SHEET

Study title: Headaches as a symptom in epilepsy

Introduction:

Good day, my name is Dr Dendere. I am required to conduct research as part of my studies in my Masters of Medicine Degree in Neurology at the University of the Witwatersrand, Faculty of Health Sciences, and Department of Neurology.

Invitation to participate: I am inviting you to take part in this research study .

What is involved in the study?

The aim of the study is to determine whether an association exists between headaches and epilepsy. You will be asked a number of questions about your condition (epilepsy) and whether you have headaches. This will be in the form of a questionnaire that will be conducted during your routine epilepsy outpatient review dates and it will take a few minutes to complete. A total of 200 patients are taking part in the research. Standard procedures being done will only be those that are routine for epilepsy, no procedures will be done for the study.

Risks: There are no risks anticipated

Benefits: If after completing the study there is an association identified between headaches and epilepsy this may be used to improve the management of both conditions.

Participation is voluntary: Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may discontinue participation at any time without penalty or loss of benefits.

Reimbursements: There are no "out of pocket" expenses.

Confidentiality: Efforts will be made to keep personal information confidential. A separate master sheet of all participants' details will be compiled for researcher use only. Data will then be processed anonymously into a computerized system that will be kept for two years if published or six years if not published, after this period the data will be destroyed.

The study has been approved by the Human Research ethics Committee HREC (Medical) with the following contact details:

Prof P Cleaton Jones Tel 0117172301 Email:
peter.cleaton-jones@wits.ac.za

Ms Z Ndlovu Administrative Officer 0117172700/1234/1252 Email: zanele.ndlovu@wits.ac.za

If you have any questions about the study, please feel free to ask them now or at anytime throughout the study by contacting the lead researcher:

Dr C Dendere
0114884911
Department of Neurology
Catherine.zyambo@yahoo.com

R14/49 Dr Catherine Dendere

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M141007

NAME: (Principal Investigator)	Dr Catherine Dendere
DEPARTMENT:	Department of Neurology Chris Hani Baragwanath Academic Hospital Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Headaches as a Symptom in Epilepsy
DATE CONSIDERED:	31/10/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Girish Modi

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 12/10/2016

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 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, 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 October and will therefore be due in the month of October each year.

Principal Investigator Signature

Date 12/10/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Demographic data (Appendix 1)

Ethnic group	
Age	
Gender	
Marital status	
Occupation	
Professional General worker Pensioner Student Unemployed	

Epilepsy history (appendix 2)

Variable
Family history of epilepsy:
yes
no
non-specific
Type of seizure:
generalized
partial
other
Age of onset:
<18
18-54
55+
Non-specific
Seizure pattern:
single
cluster
mixed
Non-specific

Cardinal rhythm:

day

night

mixed

Non-specific

Provoking factors:

yes

no

Non-specific

Median number of seizures in previous month

Non-specific

Disease duration in years

Non-specific

Current antiepileptic medication

Special investigation:

EEG

CT scan

Headache history (appendix 3)

Headache type:

Migraine

Unclassified

Chronic Tension type headache

Other

Intensity of pain:

Mild

Moderate

Severe

Non-specific

Duration of pain (hours):

<4

4-24

>24

Non-specific

Median number of attacks/month in previous year

Median number of headache days/month

Disease duration (years)

Special investigations:	
EEG	
CT scan	

Comorbidity by headache type (appendix 4)

Headache type	Without comorbidity	Pre-ictal	Ictal	Post-ictal
Migraine				
Unclassified				
Chronic tension type headache				
Other				

Co-morbidity by seizure type (appendix 5)

Seizure type	Without comorbidity	migraine	Unclassified	Chronic tension type	other
Generalised: well controlled					
Generalized: poorly controlled					
Partial: well controlled					
Partial: poor controlled					

3. RESEARCH ARTICLE

HEADACHE AS A SYMPTOM IN EPILEPSY

Authors: Dendere C and Modi G

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Abstract:

Introduction

Seizure associated headaches have been reported to occur frequently in epileptic patients. This has resulted in additional disease burden for these patients. Characterisation of seizure-associated headaches are however infrequent.

Aim

The purpose of the study is to characterise headaches as a symptom/feature in patients known with epilepsy.

Method

Over a period of six months, 200 epileptic patients from our tertiary epilepsy outpatient clinics were recruited. They answered questions from a semi-structured questionnaire regarding their seizure profile, and whether or not they had headaches. The features and characteristics of the seizures and headaches were analyzed.

Results

Of the epileptic patients, 45.5% n=91 had seizure associated headaches. No association was found with ethnicity (p=0.181) and employment status (p=0.431). Analysis of the total number of patients that had seizure associated headaches indicated that they comprised of; migraine like 46.1% (n=42), chronic tension type like headache (CTTH) 44% (n=40), and 9.9% (n=9) were unclassified. The most common being the peri-ictal headache (occurring before, during or after a seizure) Of all the patients recruited the prognosis was postictal (occurring only after a seizure) 32.5% (n=65), with migraine like headaches accounting for 16.5% (n=33) followed by tension type headaches with 13.5% (n=27). Headache intensity was reported as severe in 53.8% of all seizure associated headaches.

Conclusion

Seizure associated headaches occur commonly in epileptic patients. They are either migrainous or tension type like in character, of moderate to severe intensity and lasting

duration of 4-to-24 hours. Temporal relation to seizures is usually postictal. Headaches therefore add to the burden of symptomatology and morbidity in epileptic patients, so we recommend that physicians who manage epileptic patients specifically, should inquire about and manage epilepsy-associated headaches. Further prospective studies are needed to better understand and characterize the role of primary headaches in epileptic patients.

Introduction

Seizure associated headaches are a symptom of epileptic seizures, causing the impairment of daily living [I]. With the prevalence of migraine in patients with epilepsy ranging from 14 to 24%, and the prevalence of epilepsy in migraine subjects ranged from 1.1 to 17% [2]. The relationship between headaches and epilepsy is covered in the International Classification of Headache Disorders, Second Edition (ICHD-2) and may be associated with seizures as a preictal, ictal, or postictal phenomenon. Although rare, headache can also be the sole or predominant clinical manifestation of epileptic seizures [3]. Postictal headaches and migraine-triggered seizure, "hemicranias epileptic/' are also defined in the (ICHD-2) [4]

(Leniger T, et al) [I] Analysed the characteristics of seizure associated headaches using a prospective study. Patients in their outpatient clinics were interviewed using a questionnaire to determine whether there was a temporal succession to the occurrence of seizures in epileptic patients and headaches. They found that 34% (115) of the total 341 epileptic patients evaluated had experienced seizure associated headaches. The headaches were, 3% pre-ictal, 27% peri-ictal, and 70% postictal. Migraine like headaches accounted for 55.7% of the headaches, whereas 36.5% were tension type like headaches.

A number of research studies have however challenged the existence of a definite co-morbidity between epilepsy and headaches. (Tonini MC, et al.) [2] assessed the prevalence and clinical characteristics of epilepsy/headache comorbidity among patients from headache and epilepsy centres. The research hypothesis was that, if there 1s an association between epilepsy and headache, the prevalence of comorbidity among patients with either disorder would be expected to be higher than in the general population. [2] It was found that the prevalence of comorbidity in patients with epilepsy and in those with headache overlapped that of the general population.

The occurrence of migraine and epilepsy in the same individual has been interpreted in three ways: Firstly, migraine and epilepsy are both relatively common in the general population and therefore, occur together in some people. Secondly, migraine and epilepsy may share a pathophysiologic or genetic basis, which would explain their occasional coexistence. [5] In their paper (Papetti L, et al) [5] reviewed the relationship between migraine and

epilepsy with regard to translational research and clinical correlations and classifications. They showed that seizures and headaches share pathophysiological mechanisms.

(Forderreuther, et al).[.6.] Investigated the incidence and characteristics of seizure associated headaches and modalities of treatment. They concluded that the management of patients with epilepsy and headache comorbidity should include treatment of headache syndromes tal<lng into consideration the general guidelines for treating primary headaches.(G Mainieri, et al). [7] Established that migraine headaches were the most represented type of headache in patients with epilepsy and that post-ictal headache (post-IH) was significantly associated with both migraineur and TTH patients.

(Dana Ekstein, et a)l [9] reviewed data from clinical reports. According to the data presented in their review, post-ictal headaches (post-IH) are prevalent, clinically significant, and frequently have migraine characteristics. People at highest risk of having post-IH are young adults, both women and men, with relatively severe and longstanding epilepsy. Additional risk factors include patients that have generalized tonic-clonic. seizures (GTCSs) and a personal history of inter-ictal headaches (inter-IHs). The high risk of having post-IH, especially after GTCs, might help differentiate epileptic from clinically similar non-epileptic psychogenic spells. Particularly when taken together with fatigue. However there is not enough evidence to support the use of this association in clinical practice. [9]

Post-IHs occur commonly in generalised epilepsy mostly as migraine headaches, with inter-IH as a specific risk factor. Post-IH are underdiagnosed and undertreated, leading to self-medication. (Stephanus Schmidt Botha! et al .10.) Described the clinical characteristics of Post-IH in patients with generalised epilepsy in a tertiary hospital outpatient clinic. An observational, cross-sectional design study was conducted. Two hundred patients with generalised epilepsy were recruited from the neurology clinic at the Steve Biko Academic Hospital, a tertiary care facility in Pretoria, South Africa. Patients meeting the criteria for generalised epilepsy according to the (ILEA) were enrolled into the study. Patients participated in a semi-structured interview. Data collected included information regarding demographic, seizure and headache characteristics, medication usage, and localisation and accompanying symptoms. Patients indicated if they self-medicating for the pain of Post-IHs or whether a doctor had prescribed medication.

The study confirmed that post-IHs in patients with generalised epilepsy is a common occurrence. From the total of two hundred recruited patients with generalized epilepsy, 52% (104) were found to have post-IHs. Among the subjects with post-IHs, the majority 63% reported experiencing headache after every seizure, with severe headache lasting up to 24 hours. The majority of patients' headaches (60%) could be classified as either migraine or probable migraine indicating an association between generalised seizures and migraine post-IHs headache. No significant associations with the type of seizures, age or race and the post-IR type was found.

Aim

The aim of the study was firstly to characterise the presence and type of primary headaches as a symptom/feature in patients with epilepsy. Secondly, it was to determine if there is an association between the presence and subtype of headache and the temporal relation to seizure subtypes in epilepsy, that exists in patients attending tertiary epilepsy outpatient clinics in Johannesburg, South Africa.

seizures, demographics and headache subtypes. Included was the analysis of association of headaches and seizure control.

Results

Two hundred epileptic patients were recruited. Eighty five percent 85% of whom were between the ages of 18 and 54 years old, and 15% were greater than 54 years in age. Of the patients: 62% (n=124) were female and 38% (n=76) were male; 65.5% were of African ancestry, 14.5% were Caucasian, 11% Mixed Ancestry and 9% Asian (p=0.181) this is however a hospital based bias.

Of the epileptic patients recruited: 92% (n=184) had generalized seizures (3 of whom had absence seizures) and 8% (n=16) had partial or focal seizures. 45.5% (n=91) had seizure associated headaches (temporally related to their seizures as pre-ictal, peri-ictal and post-ictal headaches) and 25% (n=50) of the reported headaches had no temporal relation to the seizures (i.e. inter-ictal headaches). Regarding patients with seizure-associated headaches, migraine like headaches accounted for 46.1% (n=42), tension type like headaches for 44% (n=40), and 9.9% (n=9) were unclassified. Female patients with seizure associated headaches, accounted for 30.5% (n=61) of the total number of patients recruited. There was no significant gender association with seizure-associated headaches (p=0.324). The same was found for employment status (p=0.431).

The majority of patients, 93.4% (n=85), experienced less than ten seizures in the previous month, and no statistical association was identified between an increased number of seizures in the previous month to an increased likelihood of having seizure associated headaches (p=0.785).

TABLE 1: a, classifies seizure associated headaches by type and pain intensity in patients with epilepsy; b, classifies seizure associated headache by type and duration in patients with both epilepsy.

Severity		Unclassified	Migraine	TTH	Total
Moderate	Count	0	8	8	16
	% of Total			8.8%	17.6%
Mild	Count			16	26
	% of Total			17.6%	28.6%
Severe	Count			16	49
	% ofTotal		28.6%	17.6%	53.8%

Headache duration	Unclassified	Migraine	TTH	Total
<4hours	3	21	29	53 (58.2%)
4-24hrs	4	18	9	31 (34.1%)
>24hrs	2	3	2	7 (7.7%)

Table 2: Distribution of headache types and epilepsy syndrome in patients with seizure associated epilepsy.

	Migraine	Unclassified	TTH
Generalized seizures	37 (40.7%)	7 (7.7%)	38 (41.8%)
Partial/focal seizures	5 (5.5%)	2 (2.2%)	2 (2.2%)
Tota	42 (46.2%)	9 (9.9%	40 (44.0%)

Table 3: Temporal distribution of headaches for each of the headache subtypes, in patients with seizure-associated headaches.

Headache		Migraine	Tension type	Unclassified	Total
Pre-ictal	Count	7	9	1	17
	%of Total	3.5%	4.5%	0.5%	8.5%
Inter-Ictal	Count	2	4	1	7
	% of Total	1%	2%	0.5%	3.5%
Post-ictal	Count	33	25	7	65
	%of Total	16.5%	12.5%	3.5%	32.5%

Discussion

Headaches are often ignored as a symptom of epilepsy. This is because other symptoms such as disturbance in consciousness or motor phenomenon are perceived as more important [1]. What we demonstrate in the current study is that headaches form a significant burden of morbidity in the context of epilepsy.

The current study indicated that (45.5%) close to half of the epileptic patients recruited from our tertiary epilepsy clinics experienced seizure associated headaches, and a further quarter (25%) of patients had headaches temporally independent of seizures. These results are in keeping with results of previous similar studies, where (Leniger T, et al.) [1] found that peri-ictal headaches occurred in 34% of patients with epilepsy, and 42% was observed by Forderreuther et al. The current study demonstrates no statistically significant association of seizure related headaches with gender, again in keeping with a number of previous studies which also reported on no associations between seizure headache type and a particular epilepsy syndrome and gender. Furthermore ethnicity and employment status were demonstrated in the current study not to be associated with the presence of seizure associated headaches.

Within the group of patients with seizure-associated headaches, both migraine like headaches 46.1% and chronic tension type like headaches 44% occur commonly with approximately equal frequency. Our data corroborates that of the literature, in that the prevalence of the sub-types of seizure-associated headaches we found is comparable to those found by Fordereuther et al., who in their study found migraine-like headaches in 39%, and tension-type headaches in 37.5% of patients with seizure associated headaches. Furthermore additional support from the literature is through the work of (Leniger T et al) who found migraine-like headaches in 55.7% of the patients with seizure-associated headaches, and tension-type headaches in 36.5% of patients with seizure associated headaches [l].

In previous retrospective studies, peri-ictal headaches were found to occur in 28-to-47% of adult epileptic patients. These peri-ictal headaches tend to be migrainous or tension-type like

in character [11]. We found our study supports this data, in that approximately a third of our epileptic patients have peri-ictal headaches (32.5%), and that of these peri-ictal headaches, migraine like headaches account for 16.5% and tension type like headaches for 13.5% of the total and that both subtypes occur with notable frequency. Our findings are in line with previous reports in literature in which post-ictal headaches prevalence ranges from 12-to-52 % [7]. (Stephanus Schmidt Bothal, et al) [10] found that out of the total of two hundred recruited patients with generalized epilepsy 52% had postictal headaches. The majority of patients' headaches in their study (60%) could be classified as being either migraine or probable migraine in type.

Headache intensity is an important factor to assess in patients with epilepsy-associated headaches, headache intensity in our study was reported as severe in 53.8% of all patients with seizure-associated headaches.

We found no association between an increased number of headaches in the previous month to an increased likelihood of having seizure associated headaches 93.4% of patients experienced less than ten seizures in the previous month. These results contrast with the results obtained by Fernando TG et al., who found that epileptic patients with :frequent seizures had a greater tendency for the occurrence of headaches [8].

More prospective studies are needed in African developing countries to better understand and characterize the role of primary headaches in epileptic patients, and specifically the ability of interventions to improve the disease burden.

Limitations of the current study include the limited scope of patient recruited. Patients were only recruited from tertiary epilepsy outpatient clinics, and not from less specialized clinics where many uncomplicated patients are managed, there may thus be a sampling bias toward patients with more severe symptomatology and increased polypharmacy.

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