INVESTIGATION OF BRAIN TUMOUR PATIENTS WITH HEADACHE AND NON-HEADACHE PHENOTYPES USING SEQUENCES OF MRA, MRS AND DWI TECHNIQUES

CHANGMAI MANAH CHANDRA

UNIVERSITY SAINS MALAYSIA

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By

CHANGMAI MANAH CHANDRA

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACA	Anterior cerebral artery
ADC	Apparent diffusion coefficient
Cho	Choline
Cr	Creatine
DWI	Diffusion weighted imaging
HUSM	Hospital Universiti Sains Malaysia
ICA	Internal carotid artery
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
MRS	Magnetic resonance spectroscopy
MCA	Middle cerebral artery
NAA	N-acetyl aspartate
PCA	Posterior cerebral artery
PRESS	Point Resolved spectroscopy
ROI	Region of interest
STEAM	Stimulated Echo Acquisition Mode
TE	Echo time
TR	Repetition time
TOF	Time-of-flight
VOI	Volume of interest

PENYIASATAN PESAKIT TUMOR OTAK DENGAN FENOTIP SAKIT KEPALA DAN BUKAN SAKIT KEPALA MENGGUNAKAN URUTAN TEKNIK MRA, MRS DAN DWI

ABSTRAK

Urutan spektroskopi resonans magnetik proton (MRS), angiografi resonans magnetik dan pengimejan berwajaran resapan (DWI) memainkan peranan penting dalam mengenali tumor otak dengan sakit kepala. MRS mengira kepekatan metabolit otak untuk menentukan ciri dan penggredan tumor otak dengan sakit kepala. Pengimejan berwajaran resapan menilai nilai pekali resapan jelas (ADC) yang menggambarkan kepelbagaian tisu dan keselularan tumor otak yang menggambarkan punca sakit kepala. MRA digunakan untuk memahami anatomi saluran darah intrakranial dengan aneurisme atau stenosis dalam sakit kepala tumor otak. Ketiga-tiga teknik pengimejan resonans magnetik ini adalah teknik bukan invasif. Tumor otak memulakan ketidakseimbangan dalam metabolisme otak yang merupakan faktor untuk aneurisme saluran darah intrakranial yang mencetuskan sakit kepala. Pada masa yang sama, peningkatan selular tumor ini adalah satu lagi pertimbangan untuk punca sakit kepala. Oleh itu, kajian ini bertujuan untuk meneliti hubungan daripada kesan perubahan tumor yang berkaitan dengan metabolit, kaliber saluran darah intrakranial dan selularnya yang menyebabkan sakit kepala. Dalam kajian keratan rentas ini, imej radiologi HUSM 3T MRI retrospektif PRESS MRS, MRA masa penerbangan dan imej b0 dan b-1000 s/mm2 DWI dari 2013 – 2018 tahun dipilih. Ini termasuk 77 pesakit

tumor otak dengan sakit kepala dan 61 pesakit tidak sakit kepala dipilih daripada sistem PAC dan fail kes pesakit. Selanjutnya, Pesakit dengan MRA, MRS dan DWI telah ditapis untuk analisis masing-masing. Pemprosesan manual dan pakej perisian Radiant DICOM viewer (2020 2.3), Image J dan Neuromantic v1.6.3 digunakan dengan menyediakan ROI dan kaedah anggaran dan analisis yang berbeza. Penilaian metabolit otak, kaliber saluran darah intrakranial dan nilai ADC dibandingkan secara statistik menggunakan perisian SPSS versi 23. Keputusan menunjukkan gambaran yang jelas dan lebih luas tentang pengubahan metabolit yang memberikan maklumat tentang jenis dan penggredan tumor yang berkaitan dengan sakit kepala. Penurunan tahap NAA telah menggambarkan penglibatan neuron dan peningkatan dalam tahap Cho menunjukkan peningkatan sel membran dalam teras tumor pesakit sakit kepala yang sepadan dengan nilai ADC rendah (0.65±0.46 10-3 mm2/s) dalam teras tumor yang menggambarkan selular tinggi tumor dalam pesakit sakit kepala mencetuskan sakit kepala. Akibatnya, penurunan nisbah Cho/Cr pada sisi sihat kontralateral pesakit tumor otak dengan sakit kepala telah meniru jenis ketegangan sakit kepala yang tipikal. Ini juga disokong oleh dilatasi ICA (5.03±1.40) pada bahagian tumor pesakit sakit kepala berbanding pesakit tumor otak yang tidak sakit kepala (3.31±1.81). Keputusan akhir telah mewujudkan hubungan antara perubahan dalam metabolit, meningkatkan selular dan perubahan dalam saluran darah intrakranial mencerahkan jenis sakit kepala yang memberikan maklumat berharga untuk menyembuhkan pesakit tumor otak dengan sakit kepala.

INVESTIGATION OF BRAIN TUMOUR PATIENTS WITH HEADACHE AND NON-HEADACHE PHENOTYPES USING SEQUENCES OF MRA, MRS AND DWI TECHNIQUES

ABSTRACT

The sequences of proton magnetic resonance spectroscopy (MRS), magnetic resonance angiography and diffusion weighted imaging (DWI) play a vital role in recognizing the brain tumours with headache. MRS calculates the concentration of brain metabolites to determine the characteristics and grading of the brain tumour with headache. Diffusion weighted imaging evaluates the apparent diffusion coefficient (ADC) values depicting tissue heterogeneity and brain tumour cellularity depicting cause of headache. MRA is utilized to understand anatomy of intracranial blood vessels with aneurysm or stenosis in brain tumour headache. All these three techniques of magnetic resonance imaging are non-invasive techniques. The brain tumour initiates imbalance in the brain metabolism which is a factor for aneurysm of intracranial blood vessels precipitating headache. At the same time, increased cellularity of these tumours is another consideration for origin of headache. Thus this study aims to investigate the relation from impact of tumour associated changes in metabolites, caliber of the intracranial blood vessels and its cellularity causing headache. In this cross sectional study, retrospective HUSM 3T MRI radiological images of PRESS MRS, time-of-flight MRA and b0 and b-1000 s/mm^2 DWI images from 2013 – 2018 years are selected. This

includes 77 brain tumour patients with headache and 61 non-headache patients selected from PAC system and patient case files. Further, Patients with MRA, MRS and DWI were filtered for their respective analysis. Manual processing and software packages Radiant DICOM viewer (2020 2.3), Image J and Neuromantic v1.6.3 are applied by setting up ROI and different methods of estimation and analysis. The evaluation of brain metabolites, caliber of intracranial blood vessel and ADC values are statistically compared using SPSS software version 23. The results indicate a clear and wider picture of the alteration of metabolites providing information of the type and grading of tumour associated with headache. A drop in NAA level has illustrated involvement of the neurons and the rise in Cho level displayed increase membrane cellularity in tumour core of headache patients that corresponds with the low ADC value of ($0.65\pm0.46\ 10^{-3}$ mm^2/s) in tumour core depicting high cellularity of the tumour in headache patients precipitating headache. Consequently, a decrease in Cho/Cr ratio in contralateral healthy side of brain tumour patients with headache has imitated a typical tension type of headache. This is also supported by dilatation of ICA (5.03 ± 1.40) in tumour side of headache patients compared to non-headache (3.31 ± 1.81) brain tumour patient. The final results has established a connection between the changes in metabolites, increase cellularity and changes in the intracranial blood vessels enlightening the type of headache that provides valuable information to cure brain tumour patient with headache.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

The human brain is considered extraordinary with well-developed cerebral cortex constituting major component of the brain endowed with billions of nerve cells. It is a complex organ that possesses distinct inference entity accompanying complicated nervous system. Human beings are organized and inculcate features of high order cognitive capacity.

The brain tumour originates from various types of cells of the central nervous system. There frequency of occurrence is very limited and diversified genetically and biologically. The etiological factors of most brain tumours are still unresolved. They arise inside the cranial cavity from brain tissue and surrounding meninges.

According to Central Brain tumour registry of the United States (CBTRUS) the occurrence of primary malignant and non-malignant brain tumour from years 2013-2017 was recorded as 23.79 per 100,000 persons (Ostrom et al., 2020). In Malaysia, the brain tumours are sporadic. They represent 1.96% among all the malignancies. According to statistical analysis report of cancer prevalence in Malaysia by ministry of Health in 2006, the brain tumours are rank 10^{th} in their incidence with rate of 3.6% in

males. But females with incidence rate of 2.6% stand in 9th position (National cancer registry; Ministry of health, Malaysia. 2006).

The brain tumour accounts for 2% of the total mortality when compared with various types of cancers. In United States, the mortality rate of the primary brain tumour patients annually is 4.4 per 100,000 populations. The five year survival rate of 35 % is recorded for the malignant brain tumours. In children as far as 14 years of age brain is the frequent place of development of tumour. They are followed by adolescents and adults. Age is an important factor in survival rate of a patient(Wrensch, Minn, Chew, Bondy, & Berger, 2001).

Pain leads to unpleasant sensory and emotional experience in a person. Headache is one type of pain affecting a large number of populations and becoming a health problem. Stress is one of the conditions which may lead to headache. It also occurs in emotional distress person and in majority associated with medical disorder. It can also aggravate to other health complication. People complaining of headache find it difficult to continue their work regularly. The World Health Organization (WHO) reports that almost half of all adults worldwide will experience a headache in any given year. An individual with brain tumour is one of the dreaded factors of headache. The headache in brain tumour is recorded in 31% to 71% of patients (Vazquez-Barquero et al., 1994). The brain tumour headaches are associated with various neurological deficits like seizures, nausea, vomiting, change in individuality, blurring of vision and papilledema (Christiaans, Kelder, Arnoldus, & Tijssen, 2002; Loghin & Levin, 2006).

In the absence of intracranial pressure, the brain tumour headaches are placid and less likely to cause associated neurological symptoms. A headache with a diversification mimics an underlying brain tumour. The brain tumour headache is classified under secondary type of headache and is described in International Classification of Headache Disorders (ICHD - II). However, to scrutinize secondary type of headache, there are factors to be considered. It should be a space occupying lesion, a hydrocephalus or inflammation of meninges due to malignant brain neoplasm. The headache should worsen with the progress of the disease or reduced following corticosteroid therapy. As stated in ICHD – II, the secondary type of headache features aggravating nausea and vomiting in the morning hours of the day or associated with Valsalva maneuver (Pfund, Szap, Pfund, & Szapary, 1999).

The brain tumours are separated as benign and malignant. The confirmations on locations of the tumours are necessary which includes intra-axial, extra-axial and intra-ventricular tumours (Wilms, 2005). These tumours when arises from brain parenchyma are known as intra-axial tumour. The intracranial brain tumour that originates from outside the brain tissue like meninges, calvarium, ventricles, choroid plexus, pineal gland and pituitary gland are extra-parenchymal or extra-axial tumour (Demir, Onat, & Urgun, 2014). The tumours from the wall of the ventricles of the brain, from their lining or structures forming them are regarded as intra-ventricular tumour (Patnaik, Mishra, & Senapati, 2017). The headache patients always have an anxiety of having a brain tumour. Extra-axial tumours like meningioma stimulate headache with associated neurological deficits (S. Thust & Kumar, 2019). The intra-axial tumours

often provoke progressive type of headache which is often seen in tumours like glioblastomas and astrocytoma. The headaches in intra-ventricular tumours are not uncommon and well recorded which is related to compression of ventricles interrupting in the flow of cerebrospinal fluid (CSF) (Honing & Charney, 1982).

The headache in brain tumours arise due to stretching of meninges along with blood vessels supplying brain and compression of cranial nerves leading to pain (Dalessio, 1978). The headache is seen as a complaint in 63% to 83% of the tumours of the posterior cranial fossa but it is an unusual problem in cases of supratentorial tumours. They are terrible in early morning provoked by coughing and positional change. These headache were more prevalent in elderly than in children and young adults (Goffaux & Fortin, 2010; Kirby & Purdy, 2014; Suwanwela, Phanthumchinda, & Kaoropthum, 1994). The degree of headaches in metastatic brain tumour and primary tumour is almost similar. The tension type is the most common phenotype and their progression is related to extent of peritumoural oedema (Pfund et al., 1999). These headaches also pretend to be of other category like exertional, stabbing and cluster type (Mascellino, Lay, & Newman, 2001; Porta-Etessam, Ramos-Carrasco, Berbel-Garc\'\ia, Mart\'\inez-Salio, & Benito-León, 2001). The headaches were directly related to increased intracranial pressure. (Loghin & Levin, 2006). There are a total of 51.1 million headache patients in United States visiting hospital for neuroimaging from 2007 to 2010 (Callaghan, Kerber, Pace, Skolarus, & Burke, 2014). The headache patients with less incidence of malignant brain tumour signify a challenging

randomized, controlled, clinical trial. Headaches with brain tumour and the presenting symptoms in adult and children are the redflags to perform neuroimaging.

The imaging of brain is an exploratory approach that authorized visualization of anatomy and organization of human brain in vivo. It displays perfect set up and multidimensional findings related to make up, activities and alteration in framework of brain. It also provides information on physiology and metabolic profiles of the central nervous system. For the brain imaging, two methods are employed to understand the brain. The structural imaging helps to conceptualize the brain injury and intracranial pathologies whereas the functional imaging aids in illustrating metabolic abnormalities. The various neuroimaging techniques ought to be non-invasive that can keep an eye on the therapeutics encouraging good management policy (Brammer, 2009; Anuj Sharma & Weintraub, 2017). Neuroimaging techniques have been considered as a link between neurophysiological studies and clinical findings. It is one of the perfect instruments that can analyse regularity of pain and idiopathic headache. Neuroimaging has given a remarkable impression in headache investigation that often related to functional changes in the brain(May, 2012).

One of the methods of neuroimaging that has promoted extraordinary support in diagnosing the brain tumour is MRI. The MRI is a noninvasive technique assist in capturing cross sectional images of the brain by generating magnetic fields and radiofrequency pulses. The discovery of MRI illustrates a great achievement in medicine in identifying organs and structures inside human body.

The magnetic resonance spectroscopy is one of the modalities of MRI that detects the level of metabolites of the brain. The proton magnetic resonance spectroscopy ^{1}HMRS advances as a major research instrument in clinical neuroimaging. The adequacy of MRS has been evidenced in recognizing brain tumours, metabolic conditions of the brain and infections of the brain tissue.

Magnetic resonance angiography (MRA) is a noninvasive investigation performs to see the blood vessels of the brain, heart and different parts of the body. The MRA is an innovation in technology and advance in imaging techniques which is helpful for the physician to diagnose certain diseases. It depends on the intrinsic magnetic fields of tissues and blood rather than infusion of harmful chemicals in the body. The time of flight (TOF) is the most common method used in non- contrast enhanced angiography. In TOF the venous circulation is smothered for good visualization of the arteries. To visualize the intracranial blood vessels for their tortuosity with a high spatial resolution, 3D TOF is the investigation of choice (H. Tang et al., 2019).

1.2 Problem statement of the study

Patients with headache complain with pulsatile pain in the head (N. P. Young, Elrashidi, McKie, & Ebbert, 2018). The pain begins with factors such as stress, weather, hormonal fluctuations, sleep disturbances, meal skipping and sensory overload, (Kelman, 2007; D. Levy, 2009). A brain tumour is one of the frequent dreaded factors of headache and myriad of patients present complains with an underlying tumour(Goffaux & Fortin, 2010). The brain tumour headache accompanies with other neurological presentation which includes altered personality, nausea, vomiting and blurred vision(Christiaans et al., 2002). However, it is arguable that mechanism responsible for headache in brain tumour patient is either way linked to the process giving rise to primary headache (Kuntz et al., 1992).

MRI is one of the key imaging tools to identify the brain tumours. It provides perfect information to decide and outline treatment by observing the effectiveness of the management by forecasting good prognosis. However, conventional structural MRI has a restricted scope to distinguish two variety of intra-cerebral tumour since they look alike(Andres Server et al., 2010).

The MRS spectroscopy is one of the modalities of MRI that is free from hazards and is more methodical compared to conventional MRI(Peet, 2014). It is a key procedure to understand the classification and grade of brain tumour. MRS furnishes details of brain tissue metabolites and measures their concentrations illustrating

membrane changes(Bulik, Jancalek, Vanicek, Skoch, & Mechl, 2013a). It facilitates recognition of metabolites in normal and disorders in the brain(Bradley WG, 2007). MRS is valuable in proposing a definitive judgment in advance prior to pathologist comments (Tumors, Julia, & Aru, 2014). However, there are challenges in utilization of MRS in making resolution on management of the tumour which can be concluded by a simpler representation of the spectrum to identify the lesion for brain tumour treatment (García-Figueiras et al., 2016).

The blood flow in brain is maintained by communicating branches from the carotid and Vertebrobasilar system of arteries. The circle of Willis (COW) is a vital organization of arteries attributes to this collateral circulation. In cerebrovascular disorders, the circle of Willis (COW) reduces injury by providing adequate blood flow by rearranging the blood circulation to the damage region (Bisschops, Klijn, Kappelle, Van Huffelen, & Van Der Grond, 2003). Magnetic resonance angiography (MRA) is a frequent noninvasive method of MRI used to visualize the blood vessels of the brain. It is a method most commonly utilized to detect aneurysm or stenosis associated with the brain tumour headache. Even though numerous studies were performed on intracranial and extracranial blood vessels disorders, hardly one or two research with MRA has been recorded with brain tumours associated with headache (Kadota, Nakagawa, & Kuroda, 2010a).

The progression of a brain tumour indicates collapse of blood brain barrier not giving a clear picture of altered structure during its advancement which is usually

noticed during MRI(Brandsma & van den Bent, 2009). An investigation of the tumour can be approach by understanding the type of brain tissue, associated sensitivity and atypical transformation within a tumour. A biopsy is an invasive method and an inappropriate microscopic identification of the brain tumour is possible if the selection of area for collection of tissue sample is not proper(Kelly et al., 1987; Kono et al., 2001). For this study, DWI is a perfect noninvasive tool to recognize the peculiar changes in the tissue related to the tumour(Okamoto, Ito, Ishikawa, Sakai, & Tokiguchi, 2000).

The collaborative findings of DWI, MRS and MRA build up strong justification towards identifying a tumour. A quantified ADC values from the substance of the tumour along with selective ratios of the metabolites traced by MRS put in more information in distinguishing and grading of the brain tumour rather using the details solely. There is a hypothesis that the information from combination of these two techniques enhances the analysis of MRI(Tayfun & Taner, 2003). A limited number of studies have been performed combining these two techniques to understand the infrastructure of the brain tumour.

1.3 Research Questions

1. How do the Point resolved spectroscopy (PRESS) MRS, time-of-flight MRA and DWI estimate the metabolite level, caliber of intracranial blood vessels and cellularity of the tumour in headache brain tumour patients?
2. Can PRESS MRS and ADC values from DWI evaluate the differences between the high grade and low grade brain tumour causing headache from the acquired image data in USM hospital?
3. Can the anatomical changes of the caliber of intracranial blood vessels visualized in time-of-flight MRA relate changes in vascularity to the brain tumour with headache?
4. How do these data from radiological methods compare when constructing the ROI based on understanding of metabolites, caliber of the blood vessels and ADC values between tumour core and contralateral healthy side in brain tumour headache patients?
5. What are the similarities and differences in metabolic profile, caliber of blood vessels and ADC values between headache and non-headache brain tumour patients specified in this study based on previous studies using the sequences of MRS, MRA and DWI?

1.3 Objectives of the study

1.3.1 General objective

To analyze the metabolites, vascular and cellular changes of brain in brain tumour patients with headache and non-headache phenotype.

1.3.2 Specific objective

1. To quantify and compare N-acetyl aspartate, choline, creatine and other metabolites and their ratios in tumour core and contralateral healthy side of headache and non-headache brain tumour patients by magnetic resonance spectroscopy (MRS).
2. To determine and compare the intracranial blood vessel diameter changes using Magnetic resonance angiography (MRA) between tumour side and contralateral healthy side in headache and non-headache brain tumor patients.
3. To investigate the cellularity of brain tumour by analyzing the apparent diffusion coefficient (ADC) values retrieved from diffusion weighted imaging (DWI) between tumour core and contralateral healthy side in headache and non-headache brain tumour patients.

1.4 Rationale of the study

The knowledge of a particular disease is very important for physician to diagnosis and treatment. The advances in understanding a disease properly can be achieved by an innovative research. The present study is conducted to find out usefulness of sequences of MRS, MRA and DWI to identify the cause and type of headache in brain tumour headache patients by estimating the metabolic profiles, caliber of blood vessels and the cellularity of tumour. It will empower a positive outlook by verifying a connection that exists between changes in metabolites and cellularity of brain tissue in differentiating high grade tumour causing headache which will help in their diagnosis and treatment. It will also narrow the gap by acknowledging that the changes in the caliber of intracranial blood vessels associated with brain tumour is linked to tumour cellularity and metabolic ratios. A new light in monitoring and propagation of the patients with brain tumour headache will help in clinical diagnosis providing inclusion or outcome measures for trials.

1.5 Research Hypothesis

1. There is significant change of N acetyl aspartate, choline, creatine and other metabolites levels in tumour core than contralateral healthy side in headache patients compared to non-headache brain tumour patients.

2. There is more prevalence of vasospasm and vasodilation of the blood vessels of the cranial cavity in the tumour side than non tumour side of headache patients compared to non-headache brain tumour patients.

3. There is more alteration of cellularity in brain tumour than contralateral healthy side in headache patients compared to non-headache brain tumour patients.

4. There is association of alteration of metabolites of the brain, caliber of the intracranial blood vessels and cellularity of the brain tumour precipitating headache in brain tumour patients with headache.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Introduction

The chapter 2 will provide concise information on introduction to magnetic resonance imaging. This will be preceded by information and review on magnetic resonance spectroscopy (MRS), magnetic resonance angiography (MRA) and diffusion weighted imaging (DWI). It will explain the purpose of implementation of the methodology in this study that include brain tumours identification and grading using three different types neuroimaging modalities. Eventually, the fundamentals and integrity of different neurochemicals of the brain, caliber of the intracranial blood vessels and cellularity of the brain tumour with values of afferent diffusion coefficient (ADC) will be reviewed.

2.2 Approach to Literature search

An online platform was used to find the literature for this research. The different types of search engines were employed which includes Google, Google scholar, PubMed, Uptodate, Science direct, Springer online and Wiley Online Library. The articles published in English or English version were explored for this study.

The exploration of literature review advanced gradually from basic articles to more groundbreaking studies. The keywords used to begin search are “brain tumour and headache” followed by “brain tumour and MRI”. Successively, the advanced keywords like “Brain tumour and MRS”, “brain tumour and MRA and “brain tumour and DWI” were entered to retrieve the information. A correlation of findings in brain tumour using different modalities of MRI are searched with keywords like “brain tumour MRS and DWI”, “brain tumour MRS and MRA” and “brain tumour MRA and DWI”. Further, the findings of the studies with a specific brain tumour and a specific MRI technique were explored with keywords, for MRS “Meningioma, headache and MRS”, “Glioma, headache and MRS” and “Metastatic brain tumour, headache and MRA. Similarly for DWI the keywords used are “meningioma, headache and DWI”, Glioma, headache and DWI and “pituitary adenoma, headache and DWI”. In addition to that for MRA, keywords with specific intracranial artery and brain tumour entered to find the articles. This includes “Internal carotid artery, headache, meningioma and MRA, “Middle cerebral artery, headache, glioma and MRA and “anterior cerebral artery, headache, Medulloblastoma and MRA”. Additionally other major arteries forming circle of Willis with specific brain tumour and headache are entered as keywords to find articles.

2.3 Brain tumours and headache

A patient with brain tumour exhibits distinctive signs or symptoms, an unveiling complain of headache is always a reason of worriment for patient and doctor. A judgment to examine the headache is crucial that involve many complications

comprising of time therapeutic value, clinical confidence and constraints. The neuroimaging of the brain tumour patient will secure confidence among doctors by ruling out any underlying pathology. A proper identification of the brain tumour and grading is necessary for good management and recovery (Kernick et al., 2008). For this a noninvasive procedures are rather supportive for observing the cell transformation, changes of metabolites and intracranial blood vessels (Ro et al., 2020). In noninvasive technique modalities of magnetic resonance imaging (MRI) plays a vital role to identify the brain tumour associated with headache. Proton magnetic resonance spectroscopy (MRS) is a non-invasive procedure that quantifies the levels of brain metabolites (Chiang et al., 2018). Magnetic resonance angiography is one of the essential methods to illustrate the intracranial blood vessels (Wrede et al., 2014). Diffusion weighted imaging provide the apparent diffusion coefficient values depicting tissue heterogeneity (Sui et al., 2016). Headache is common symptom in brain tumour patient. There is link between headache and changes in metabolites, alteration in intracranial blood vessels and tissue cellularity in brain tumour patients. To break the curiosity of understanding the reason behind headache in intracranial tumours, brain tumour patient are selected for this study.

Many cases of headache are encountered in outpatient clinic and Emergency Department for a proper diagnosis. For identification of these headaches a perfect choice of neuroimaging techniques like Magnetic resonance imaging (MRI) is required. The main purpose for performing neuroimaging in headache patient is to discover the prime source of their origin (Jensen & Stovner, 2008; Aseem Sharma et al., 2013). The

brain tumours such as malignant glioma and brain metastasis have poor survival rate and disappointing prognosis. However their conditions can be improved through different mode of management like surgery, chemotherapy and radiation. This is only possible by spotting these tumours by neuroimaging providing a guiding to repositioning the treatment (Gleason & Devaskar, 2012). An early approach of neuroimaging in patients with first time headache show low incidence of malignant brain tumour. This contemporary exercise of neuroimaging hardly ever skips recognition of the brain tumour. It was recorded that neuroimaging in each 1000 headache patients expresses malignant tumour in 3.3% individuals. From this 2.6% would be identified in first 90 days and 0.5% numbers of cases following one year (Carey, Callaghan, Kerber, Skolarus, & Burke, 2019).

The opinion from the studies categorize brain tumour headache based on their frequency, intensity, duration and its nature. It is also dependent upon precipitating factors and position of the tumour (Forsyth & Posner, 1993). The characteristic of headache and its link with brain tumour pathology need to be understood. A preexisting headache is a condition determining prevalence of headache in brain tumour patients. However, there are instances where individual become free from headache with the brain tumours. The headache in brain tumours is often bilateral and medium to high intensity experienced towards frontal, parietal and occipital regions. The frequency of these headaches is mostly less than once weekly and in few percentage felt daily. They are associated with nausea, vomiting and blurring of vision. The majority of brain tumour headache are categorized under tension type of headache, rarely they are linked

to cluster headache and migraine. A dull type of headache is encountered notably in high grade malignant tumour like glioblastoma multiforme. However, brain tumours like meningiomas exhibits pulsating pain. This pain of pulsating nature corresponds to rich blood vessels in tumours of the meninges with trigeminal nerve innervation (Goadsby, Lipton, & Ferrari, 2002). In relation to brain tumour location, the headache is confine more in occipital region in infratentorial brain tumours. (Schankin et al., 2007). These interpretation raises concern to see a connection in mechanism inducing brain tumour headache and primary headache.

The intracranial brain tumour headaches are often bilateral, localized over the frontal region with mild pressing quality. They are infrequently associated with nausea and vomiting well relieved by analgesics. An individual with younger age have high prevalence of headache associated with brain tumour. The reason is connected to atrophy of the brain widening the subarachnoid space and the ventricles providing more room for an advancing brain tumour (Philippon, 2004). The genetic factors are essential connection to headache in a brain tumour patient. The intra-axial tumours like glioblastoma are frequently related with complains of headache. The fast advancement of the glioblastoma prevent adjustment of the organized pain sensitive structures due compression by the tumour stimulating headache. The pituitary adenoma an extra-axial tumour simultaneously precipitates headache which is connected to their neuroendocrine mechanism (Miles J. Levy et al., 2004). The intra-ventricular brain tumours are the frequent cause of headache connected to obstruction in the flow of cerebrospinal fluid. The intra-ventricular tumours are primary and secondary. The

primary tumours includes choroid plexus carcinoma, choroid plexus papilloma, ependymoma and meningioma (Han, Lee, Kim, & Kim, 2019). The headache related to intracranial tumours are familiar complain. The origin of headache is associated with the location and volume of the brain tumour. A change in level of metabolites, caliber of the intracranial blood vessels, associated with alteration of tumour cellularity frequently arise question related to precipitation of headache in brain tumour patients. Malaysian population confronting increasing incidence of brain tumour cases annually.

World Health Organization (WHO) classification of brain tumour 2016

Table 2.1 Brain tumour grading (intra-axial) based on WHO classification 2016

	Intra-axial tumour	Grade
1	Diffuse astrocytic and oligodendroglial tumour	
i	Oligodendroglioma	II
ii	Anaplastic Oligodendroglioma	III
iii	Glioblastoma-IDH wild type	IV
2	Other astrocytic tumours	
i	Pilocytic astrocytoma	I
ii	Pleomorphic xanthoastrocytoma	I
iii	Anaplastic pleomorphic xanthoastrocytoma	III
3	Ependymal tumour	
i	Subependymoma	I
ii	Ependymoma	II
iii	Anaplastic ependymoma	III
4	Other Glioma	
i	Angiocentric glioma	I
ii	Choroid glioma of third ventricle	II
5	Choroid plexus tumour	
i	Choroid plexus papilloma	I
ii	Atypical choroid plexus papilloma	II
iii	Choroid plexus carcinoma	III
6	Neuronal and mixed neural-glial tumour	
i	Dysembryoblastic neuroepithelial tumour	I
ii	Central neurocytoma	II
iii	Anaplastic Ganglioglioma	III
7	Pineal gland tumour	

"Table 2.1 continued"

	Intra-axial tumour	Grade
i	Pineocytoma	I
ii	Papillary tumour of pineal region	II
iii	Pineoblastoma	III
8	Embryonic tumours	
i	Medulloblastoma	(all IV types)

Table 2.2: Brain tumour grading (extra-axial) based on WHO classification 2016

	Extra-axial tumour	Grade
1	Meningiomas	
i	Meningioma	I
ii	Atypical meningioma	II
iii	Anaplastic (malignant) meningioma	III
2	Cranial nerve tumours	
i	Schwannoma	I
3	Non-meningothelial tumours	
i	Haemangioblastoma	I
4	Sellar tumour	
i	Craniopharyngioma	I
ii	Granular cell tumour	I
iii	Pituicytoma	I
iv	Spindle cell oncocytoma	I

Table 2.3: Brain tumour and type of headache

Study reference	Study type	N	Brain tumour	Type of headache
(Forsyth & Posner, 1993)	Prospective	111	Primary and metastatic tumour	Tension type: 77%, migraine type: 9%, other types: 14%
(Schankin et al., 2007)	Prospective	85	Glioblastoma, Meningioma, Metastasis	Tension type: 39.2%
(Russo et al., 2018)	Prospective	527	Glioma	Tension type: 47%, classic brain tumour headache: 42%

"Table 2.3 continued"

Study reference	Study type	N	Brain tumour	Type of headache
(Valentinis et al., 2009)	Prospective	116	Gliomas, Pituitary adenoma, neurinomas, metastasis	Tension type: 23.5%, Migraine: 13.3%
(M. J. Levy, Matharu, Meeran, Powell, & Goadsby, 2005)	Prospective	84	Pituitary tumour	Chronic migraine: 46%, Episodic migraine: 25%, primary stabbing headache: 27%, cluster headache: 3%, Others: 19%
(Peterson, 2001)	Review		Primary brain tumour	Majority tension headache

2.4 Introduction to MRI.

The magnetic resonance imaging has contributed a monumental appreciation in medical investigation. The diagnosis of the certain diseases has become simple without exposing the patient to threatening radiations. The original introductory images of magnetic resonance imaging were first developed in Nottingham and Aberdeen in (Hawkes, Holland, Moore, & Worthington, 1980; F. W. Smith et al., 1981)

2.4.1 Principle of MRI

The magnetic resonance imaging contains four fundamental principles;

1. In the first step, the patient is positioned around a magnet.
2. In the second step, a radiofrequency pulse is generated and discharged with a coil.
3. In the third step, the signal originated from the patient is received by the coil.
4. In the fourth step, the incoming signals from the patient are converted to an image.

The conventional structural MRI is the perfect choice in diagnosing tumours of the nervous system in spite of countless advances in imaging procedures. During the procedure high intensity signals are received from the tissues in human body at a molecular level involving structures of the atom resulting in a well define image of human brain. A strong magnet capable of producing powerful magnetic field is used for MR imaging having strength ranging between 0.2 to 3 Tesla. The power of the magnet above 3 Tesla is employed for research objectives. However, for other modalities of MRI such as spectroscopy, functional MRI and cardiac MRI are workable with 1.5 Tesla or more. The power of the magnetic field is measured in Gauss and Tesla.

1 Tesla = 10kG = 10,000 Gauss

The MR imaging technique is based on involvement of protons. These positively charged particles are component of a hydrogen nucleus (H^+). Hydrogen ion are often

used because of they are plentiful in human body. There are other nuclei that can be introduced in the MRI technique-for example, fluorine (^{19}F)(Effects & Resonance, 1947). However to be a part of MRI, they must have a property of spin and ought to have a nucleus with odd number of protons. The hydrogen atom possesses a single proton that is most commonly utilized in MRI procedure. The H^+ ion is comparable with a proton. There are prolific amount of hydrogen ions in water (H_2O) present in our body. These molecules of water freely infiltrate across the tissues. The MRI with their generated magnetic field act chiefly upon water (70%) followed by fat, minerals and proteins.

2.4.2 Positioning patient in magnetic field

The motion of the protons in the patient body occurs arbitrarily in different directions without any impact of magnetic field from outside. After patient is placed in the MRI machine and exposes to an external magnetic field (B_0), the protons stop moving randomly. They aligned and spin in the direction of external magnetic field. Once the protons are oriented, they started spinning around their own axis. Simultaneously, at the same time the axis of rotation of the proton undergo motion forming a cone. This process is known as precession.

The precession of proton per second is recorded as precession frequency measured in Hertz. The frequency of precession is directly proportion to external magnetic field (B0).

This association is determine by Larmor's equation:

$$\omega 0 = B0 \times \gamma$$

Where,

$\omega 0$: precession frequency measured in Hertz

B0: Power of external magnetic field in tesla

γ: Gyromagnetic ratio measured in megahertz per tesla (constant for every atom at a particular magnetic field; example: 1H, $\gamma/2\pi$ 42.57 MHz/T)

Few values from Larmor's equation include:

Hydrogen proton in 1 Tesla: 42 MHz

Hydrogen proton in 1.5 Tesla: 64 MHz

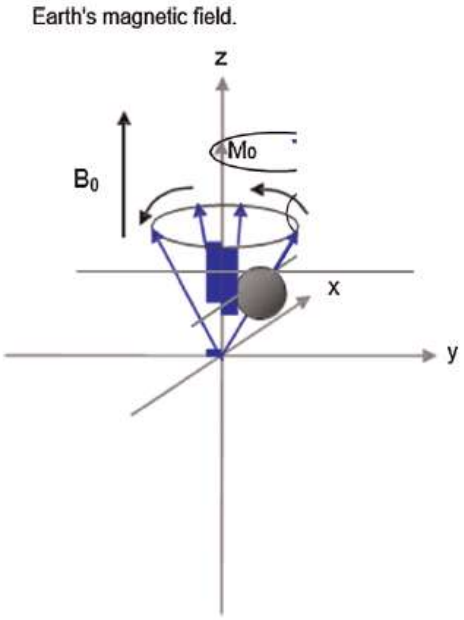

Figure 2.1: Precession of a nucleus along external magnetic field (B_0). M_0: Net magnetization direction; x, y and z illustrates Cartesian axis. (Grover et al., 2015)