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Characterization of Brain Tumour Headache Using Magnetic Resonance Spectroscopy

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ABSTRACT

Headache is frequently associated with serious illness like brain tumour. The tension type of headache (TTH) is typical and distinct from migraine and cluster headaches. The magnetic resonance spectroscopy is a noninvasive modality assist in conceptualizing the quantification of pain. The purpose of this study is to evaluate the spectrum of metabolites and understand the link between the metabolites and headache in brain tumour patients. The type of study is retrospective containing 22 brain tumour headache patients with magnetic resonance spectroscopy. The values of metabolites and their ratios from the tumour core and contralateral healthy parenchyma are recorded from the region of interest (ROI) and are analysed with non-parametric Mann Whitney U test.There is low level of N acetyl aspartate (2.32±0.82) and creatine (2.33±0.89) in the tumour core compared to their spectrum in the contralateral healthy area. The Cho/Cr ratio (0.04±0.23) in contralateral healthy area is very low compared to tumour core that describes tension type of headache (TTH). The Cho/Cr ratio variation gives a valuable indication of headache type. It illustrates the intensity of pain in individuals with brain tumour providing a guide to treatment approach.

Keywords: Brain tumour, headache, metabolites, magnetic resonance spectroscopy

Introduction

Headaches are one of the factors aggravating anxiety and depression in general population. They are extremely common and mostly primary affecting 93% of male and 99% female. An individual frequently encounter tension headache with incidence rate of 69% to 80% followed by migraine (6% - 25%) and cluster headache (0.006% - 0.24%)(Broner, Kohen, 2009). However, the secondary headaches are also not very uncommon arising from brain tumour, hydrocephalus or meningitis. These headaches are described in The International Classification of Headache Disorders (ICHD) in annex 7.4. The secondary headache worsens with the progress of the tumour and is augmented by nausea and vomiting. They are intensified in early morning along with coughing and Valsalva maneuver(Rasmussen, Jensen, Schroll, Olesen, 1991; Suwanwela, Phanthumchinda, Kaoropthum, 1994; Pfund et al., 1999). The brain tumour headaches are mostly experience bilaterally and are dull to throbbing in quality, in general linked to pre-existing headache and typically are tension type(Schankin et al., 2007).The pain encountered by an individual is too difficult to express to be determined making their studies complex and

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stretching. This divergence can be narrowed down by doing research through neuroimaging techniques.The magnetic resonance spectroscopy (MRS) is a noninvasive neuroimaging technique extremely distinguishing to trace the variations of metabolites differentiating brain tumour headache (Sherif et al., 2014). The changing pattern of metabolites in MRS is often noticed with pain. The frequent metabolites include N-acetyl aspartate (NAA), Choline, Creatine, Lactate, Alanine and Lipid. Additionally, their ratios NAA/Cr, Cho/NAA and Cho/Cr are also analyzed (Bulik et al., 2013).The present study is performed to recognize a link between brain tumour and character ofheadache by observing the spectrum of metabolites and their ratios.

Methodology

It is a retrospective study performed on brain tumour patient complained of headache. During the sampling of patient, research was refined by including brain tumour patients with headachewith their ages ranging between 5 to 70 years with diversified population comprising genders fromMalay, Chinese and Indian races. The patient'sinformation was collected from the case files (ARCHIVE) of Neuroscience Department and the radiology imageswere obtained from picture archiving and communication system (PAC) system of University Sains Malaysia (USM) hospital, Kelantan, Malaysia. A total of 22 patients with MR spectroscopy were chosen for the studywhich includes meningioma (n=9), glioblastoma (n=2), astrocytoma (n=2), pituitary adenoma (n=1), Craniopharyngioma (n=1), metastatic brain tumour (n=2), Medulloblastoma (n=2) and ependymoma (n=1). The Philips ACHEVA 3 Tesla MRI machine was used to perform the procedure. The ethical committee (JEPeM) of University Sains Malaysia confirmed the ethical approval and assigned a code USM/JEPeM/20080420 for the research. The individual who has undergone surgery, radiotherapy and having head injury are ruled out from the study. From the radiological perspective, MR spectroscopy image ofpatients displaying artifacts and disruption spectra were also precluded.A sequence of AxT1/T2/FLAIR/DWI/ADC/SagT1/post Gado/MRS/MRA/MRV was maintainin short echo time (TE: 35 ms) and repeatation time of TR: 2000. A single-voxel point-resolved spectroscopy (PRESS) with variable dimensions in voxel was practicedand normalized for contrast rationale. A highly qualified radiographer with assistance of anon duty radiologist determined the positioning of voxel forinterpretation. The NAA/Cr, Cho/NAA and Cho/Cr ratios in tumour core are recorded.Anirregular distribution of metabolites and their ratios were observed during the data collection. Hence, non-parametric Mann-Whitney U test was performed to calculate the divergence in metabolites and their ratios between ROI of tumour region and contralateral healthy region in brain tumour headache patients.The SPSS version 23 software packages were used to analyse the values of metabolitesspectra.

Result

The metabolites between contralateral healthy region of interest (ROI) and ROI over the tumor are compared in brain tumour patients with headache. The results were estimated by determining mean ± standard deviation (SD).

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Table 1: Comparison of spectrum of metabolites in headache patients between healthy and tumour ROI in single voxel spectroscopy

MRS Parameters	Healthy ROI	Tumour ROI	P Value	Mann-Whitney U
NAA	3.07±0.48	2.32±0.82	***0.00***	76(-3.62)
Cho	2.86±0.45	2.86±0.45	0.39	186(-0.85)
Cr	2.89±0.46	2.33±0.89	***0.01***	120(-2.34)
Lactate	1.57±0.36	1.61±1.49	0.65	193(-0.680)
Alanine	2.22±0.56	2.11±1.04	0.47	21(-0.44)
Lipid	2.00±0.14	2.47±0.06	0.31	0(-1)
Acetate	0.22±0.19	0.41±0.61	***0.00***	*45(-4.28)*
NAA/Cr	2.11±0.33	2.64±0.28	***0.00***	11(-2.92)
NAA/Cho	0.11±0.01	0.10±0.03	0.93	100(-0.08)
Cho/NAA	0.23±0.23	0.16±0.58	0.08	143(-1.72)
Cho/Cr	0.04±0.23	0.57±0.66	***0.00***	79(-3.39)

Table 1 contains the mean values of metabolites and their ratios detected during magnetic resonance spectroscopy. The NAA in contralateral healthy region (3.07±0.48) is higher than tumour core (2.32±0.82). The Mann-Whitney shows a result of 76(-3.62) with P value less than 0.05. Hence there is significance difference in the level of NAA between contralateral healthy region and tumour core. The spectrum of Choline is similar for contralateral healthy region (2.86±0.45) and tumour core with P>0.05. The creatine peak is high in contralateral healthy area (2.89±0.46) compared to tumour core (2.33±0.89) with a significant P value of 0.01. Therefore there is significant difference in creatine between contralateral healthy area and tumour core. The lactate level is very similar in contralateral healthy area (1.57±0.36) than the tumour core (1.61±1.49) with P > 0.05. The Mann-Whitney exhibits a value of 193(-0.680). The alanine level is higher in contralateral healthy area (2.22±0.56) than tumour core (2.11±1.04) with a non-significant P =0.47. The Mann-Whitney shows a value of 21(-0.44). The lipid is slightly increased in tumour core (2.47±0.06) and contralateral healthy region (2.00±0.14) with P= 0.37. Acetate is high in tumour core (0.41±0.61) than contralateral healthy area (0.22±0.19 with P=0.00. The Mann-Whitney gives a value of 45(-4.28). Thus there is significant difference in lactate between contralateral healthy area and tumour core. The NAA/Cr ratio is higher in tumour core (2.64±0.28) than contralateral healthy region (2.11±0.33) with a significant P value of 0.00. The NAA/Cho ratio is high in contralateral healthy region (0.11±0.01) than tumour core (0.10±0.03) withP> 0.05. The Cho/NAA ratio is higher in contralateral healthy area (0.23±0.23) compared to tumour core (0.16±0.58) and P value of 0.08. The Cho/Cr ratio is high in tumour core (0.57±0.66) than contralateral healthy region (0.04±0.23) with P= 0.00. This shows existence of significant difference in Cho/Cr ratio between tumour core and contralateral healthy area in brain tumour patients with headaches.

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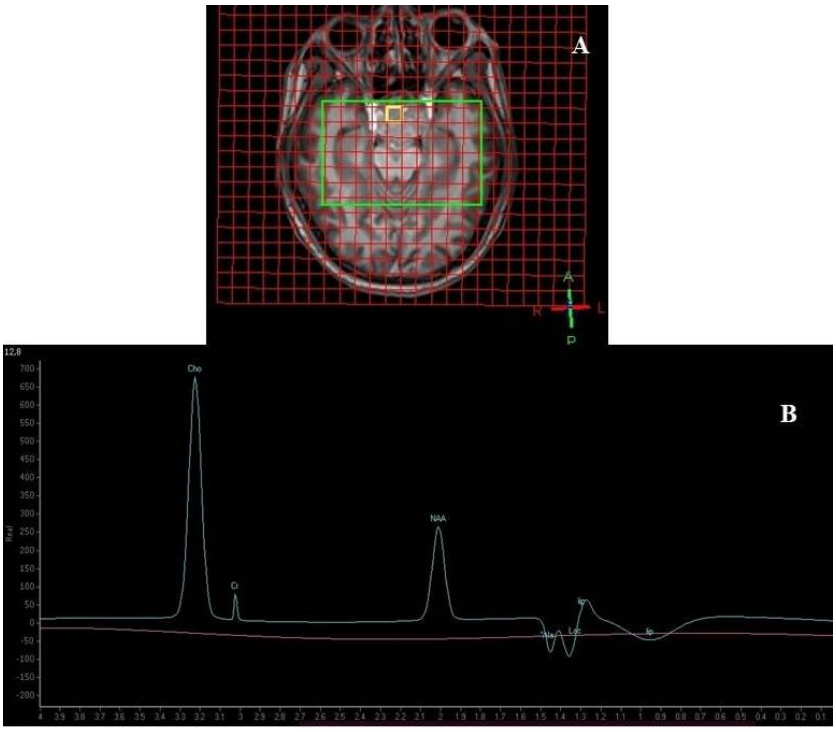

Figure 1 A 52-year-old male with features of Craniopharyngioma: An Axial FLAIR image showing (A) heterogeneously hyperintense lesion with mass effect on cerebral peduncle and midbrain. Magnetic resonance spectroscopy (MRS) from the single voxel in Region of interest (ROI) showing (B) elevated peak of Choline, low Cho/NAA and high Cho/Cr ratioin tumour core

Discussion

The brain tumour headache is tolerable to unendurable, widely bilateral experience in frontal, parietal and occipital regions. These headaches ariserepeatedly in time interval of less than a week and in one or two instances daily. They accompany with nausea, vomiting and blurring of vision. The majority of brain tumour headache predominantly classify as tension type of headache associated with primary or metastatic brain tumour which is compressing in nature and gentle to modest in type (Valentinis et al., 2009; GBD, 2017; Zhou et al., 2020). In these persistent headaches neuroimaging procedures and research discovered disturbance in excitability, biochemical and structural organization of brain. It is still unexplainable whether this attributes of neuroplasticity indicates a chronic tension type of headache(Lai et al., 2015). There are triggering factors that stimulate and precipitate brain tumour headache. Some of the factors include anxiety and depression which are often noticed in brain tumour patients. The lethargy, drowsiness, dropping attentiveness and emotional delinquency are frequently reported as manifestation of depression associated with brain tumour (Edition F, 2013; Zabel, 1995; Pranckeviciene, Bunevicius, 2015; Lucchiari et al., 2015). The incidence rate of depression related symptoms with brain tumour varies between 2% to 95% perhaps owing to consciousness of the disease and management(Fox, Lyon, Farace, 2007; Palese, Cecconi, Moreale et al., 2012). Magnetic resonance spectroscopy (MRS) is the important tool in tracking undulation of metabolites of brain in these situations for accurate proposal of management.

The concentration of N-acetyl aspartate (NAA), total choline (tCho), Cr, M-Ino, glutamine and glutamate are valuable marker to indicate a brain injury. The level of the metabolites ratio associated with creatine (Cr) has great value and significance in predicting tension type of headache. The alteration in Cho/Cr ratio is a useful indicator to suspect tension type of headache. Studies showed connection of metabolites imbalance in mood disorders like anxiety and depression with chronic headache(Mohamadi et al, 2020). However, some studies declare no change in metabolite level detected in fibromyalgia associated anxiety and depression. Interestingly, the Cho/Cr ratio variation was noticed and found to be linked to intensity of the pain (Harris et al., 2008; ,Foerster et al., 2015). In current study an altered Cho/Cr ratio is detected in headache patients with brain tumour. The Cho/Cr ratio is higher in tumour core (0.57±0.66) than in the healthy area (0.04±0.23) of the brain. Its analysis showed significant value as $p<0.05$. The result is quite similar with the findings of the previous studies that symbolize severity of the pain. The quantity of choline illustrates high cell membrane synthesis due to increase cell formation. The Cho/Cr ratio changes expresses alteration in brain metabolism. The stimulation of pain receptors from triggering factors can cause imbalance in metabolism of brain. In this study very low Cho/Cr in healthy parenchyma of the brain are affixed to high triggering factors which depicts disturbances in brain metabolism. There are evidences on low energy utilization and change in neurotransmitter modulation in patients suffered with anxiety and depression. A link between amount of choline and framework of mind had been noticed in a study on patients with chronic pelvic pain syndrome. Acetylcholine regulates relays between the synapses and proposes to be the neurotransmitter for uncertainty that boost the signal to noise ratio in the cerebral cortex from restraining outside environment inputs which do not require urgent enquires. The formation of acetylcholine from choline probably result of continued nociceptive stimulation from trigger points (Picciotto, Higley, Mineur, 2012).

The character of the headache in the present study reflects predominantly tension type of headache depending on the findings of Cho/Cr ratio. As in migraine a high lactate concentration is observed in the cerebral cortex depicting an affect in oxidative glycolysis that symbolizes disorder of mitochondria(Lin, Crawford, Barker, 2003). However, some studies on migraine concentrating on occipital cortex shows decrease NAA/ Cr ratio (Gu et al., 2008; Toldo et al., 2011). In this current study spectrum of lactate and NAA/Cr ratio doesn't reflect a migraine type of headache.

Conclusion

The secondary headaches with change in their characters often raise curiosity. The brain tumours are frequently associated with headache. A preexisting headache is one of the stimulating factors for brain tumour headache. Additionally precipitating factors exacerbate the brain tumour headache. The variability in Cho/Cr ratio is linked to trigger points and corresponds with the intensity of pain portraying tension type of headaches.Furthermore, trigger points stimulating brain tumour headache has a direct effect on brain metabolism.

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Conflict of Interest
There is no conflict of interest between the authors.

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