Proton Magnetic Resonance Spectroscopy to Detect Correlations between Clinical Symptoms and Brain Metabolite Levels in Patients with Tension-type Headache

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ABSTRACT

Background: Proton magnetic resonance spectroscopy (^{1}HMRS) is a noninvasive method to quantify pain. A ^{1}HMRS spectrum is a group of peaks at different radio-frequencies, showing proton nuclei in various chemical environments. These MR spectra provide information about metabolite concentrations, and make MRS a useful procedure to monitor metabolic fluctuations due to disease, and to track the efficacy of treatment.

Objective: This study aims to identify correlations between clinical symptoms in patients with tension-type headache (TTH) and concentrations of brain metabolites.

Material and Methods: In this observational study, twenty-four patients (4 men and 20 women) with chronic TTH were included. To evaluate their clinical symptoms, the number of trigger points, headache frequency and headache intensity were recorded. The levels of anxiety and depression were recorded with the Beck Anxiety Inventory (BAI) and Beck Depression Inventory II (BDI- II). Concentrations of brain metabolites were determined in the anterior cingulate cortex, thalamus and primary somatosensory cortex of left hemisphere with ^{1}HMRS.

Results: There was a negative correlation between trigger point count and choline/creatine (Cho/Cr) ratio in the primary somatosensory cortex [r= −0.509, n= 24, *p*= 0.01]. There were no correlations between other clinical symptoms of TTH and concentrations of brain metabolites.

Conclusion: Patients with more trigger points had a lower Cho/Cr ratio, which may indicate alterations in brain metabolic activity.

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Keywords

Brain Mapping; Neuroplasticity; Pain; Anxiety; Depression; Magnetic Resonance Spectroscopy

Introduction

Magnetic resonance imaging (MRI) offers advantages such as accessibility, contrast adaptability, pathophysiologic specificity, and the potential for repeated studies without adverse health effects, and has thus become a method of choice in clinical practice, especially when a powerful imaging method for the brain is needed. Magnetic resonance spectroscopy (MRS), a newer modality, is the

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most widely available noninvasive method to evaluate cellular metabolism and monitor neurometabolic disorders [1].

However, MRS is limited to the analysis of specificregions of interest in areas much larger compared to those amenable to the level of resolution provided by MRI (typically 1–10 cm^3 for MRS vs. 1–10 mm^3 for MRI). An MRS spectrum is a group of peaks at different radiofrequencies, which show proton nuclei in various chemical environments. In these spectra, the area of resonance is considered relative to the chemical concentration [1].

Because it is able to provide information about the chemical composition of the brain, MRS can be used to evaluate neural systems [2]. This technique can usually detect small molecules at concentrations of 0.5–10 mM within cells or extracellular spaces. Magnetic resonance spectra thus provide information about metabolite concentrations, making MRS a useful procedure to monitor metabolic fluctuations due to disease, and track treatment efficacy. Several metabolites can be detected with various nuclei for spectroscopy, such as ^{1}H, ^{31}P, 19F, ^{13}C and ^{23}N. Hydrogen (^{1}H) MRS($^{1}HMRS$) is the main method in biomedicine because of its sensitivity, availability, and the presence of readily detectable^{1}H nuclei in most metabolites [3]. Accordingly, $^{1}HMRS$ has currently been a well-known noninvasive method to quantify brain metabolite concentrations in the living individuals, and become a powerful assessment tool for many pathologic conditions [4].

Spectra obtained with $^{1}HMRS$ can reveal biochemical variations associated with pain states. Because the pain experience in patients is too complex to be readily quantified, both research and the management of pain are challenging. Currently this gap can be partially filled with neuroimaging techniques. For example, $^{1}HMRS$ studies have shown that treatment can decrease glutamate levels in the insula of patients with fibromyalgia. This alteration in glutamate levels was related with clinical changes and functional MRI findings in these patients [5].

In painful conditions such as low back pain [6, 7], complex regional pain syndrome [8] and neuropathic spinal cord injury pain [9], biochemical changes take place in the brain. Siddall et al., demonstrated that MRS spectra obtained in the anterior cingulate cortex, thalamus and prefrontal cortex may distinguish patients with low back pain from healthy people with accuracies of 100%, 99%, and 97%, respectively [10].

In chronic headaches, electrophysiological and neuroimaging studies have revealed changes in brain excitability, biochemistry, function, and structures. Nevertheless, according to Lai et al., "it remains undetermined whether these common features of neural plasticity can be regarded as neurologic signatures for chronic headaches" [11].

In the present study, we aimed to identify correlations between clinical symptoms, including trigger point count, headache frequency and intensity, anxiety and depression in patients with tension-type headaches (TTH), i.e. the most prevalent type of headache [12], and the concentration of brain metabolites in the anterior cingulate cortex, thalamus and primary somatosensory cortex.

Material and Methods

Participants

In this observational study, the participants were 24 patients (4 men and 20women) with chronic TTH, recruited among patients referred to the Imam Reza neurology clinic for their headaches. Patients with a diagnosis of chronic TTH and any trigger points in their posterior cervical muscles were included in the study; patients were excluded if they had cervical disk herniation or any neurological or rheumatoid disorder, and if they were using opioid prophylaxis, antidepressant oranti-anxiety drugs, or if they were pregnant or breastfeeding. All participants signed a consent form

before entering the study.

Procedure

To evaluate clinical symptoms, the number of trigger points was recorded for each participant, along with self-reported intensity and frequency of headaches during the previous month. Intensity was recorded as a number between 0 and 10 on a numeric pain scale that indicated average intensity during the previous month; frequency was recorded as the number of days per month when headaches occurred. The levels of anxiety and depression were recorded with reliable, validated instruments, i.e. the Beck Anxiety Inventory (BAI) and Beck Depression Inventory II (BDI-II) [13, 14]. The BAI and BDI- II instruments both consist of 21 items evaluating the level of anxiety and depression. The total score ranges from 0 to 66, with higher scores indicating greater anxiety and depression.

To evaluate neural plasticity, the concentration of N-acetyl aspartate (NAA), total choline (tCho), creatine (Cr), myo-inositol (M-Ino), and glutamate and glutamine (GLX) were determined in the anterior cingulate cortex, thalamus and primary somatosensory cortex of the left hemisphere with ^{1}HMRS. Single voxel spectroscopy was done at 1.5 tesla (Magnetom Avanto version B19, Siemens, Germany) with a standard 12-channel circular head coil and a conventional PRESS sequence (TR/TE= 1500/30; NSA= 128). Metabolite concentrations were expressed as ratios to the concentration of Cr.

Statistical analysis

The sample size for this study was calculated as 24 patients based on a previous study [15] (α= 0.05, β= 0.2). All analyses were performed using SPSS v.21 software. A significance level of $p < 0.05$ was used for all analyses. Normal distribution of data was verified by the Kolmogorov–Smirnov test. Pearson product–moment correlation coefficients were calculated to evaluate the relationship between clinical symptoms of TTH and concentrations of brain metabolites.

Results

Descriptive data for the participants are presented in Table 1. The mean values indicate that headache intensity was moderate and the levels of depression and anxiety were mild.

The findings of the study are summarized in Table 2. Overall, there was a negative correlation between trigger point count and Cho/Cr ratio in the primary somatosensory cortex [r= −0.509, n= 24, p= 0.01]. Higher numbers of trigger points correlated with lower Cho/Cr ratios. There were no correlations between the other clinical symptoms of TTH and brain metabolite concentrations.

Table 1: Descriptive data for the participants.

Variable	Mean	Standard deviation	Number
Age (years)	39.83	14.05	24
Trigger point count	4.70	0.90	24
Headache frequency	15.41	7.62	24
Headache intensity	7.04	1.94	24
*BAI	14.54	8.49	24
**BDI- II	14.20	9.25	24
Anterior cingulate cortex			
NAA/Cr	1.74	0.31	24
Glx/Cr	0.86	0.18	24
Cho/Cr	0.77	0.09	24
MIno/Cr	0.40	0.08	24
Thalamus			
NAA/Cr	1.61	0.36	24
Glx/Cr	0.93	0.41	24
Cho/Cr	0.82	0.25	24
MIno/Cr	0.24	0.09	24
Primary somatosensory cortex			
NAA/Cr	1.43	0.29	24
Glx/Cr	1.08	0.27	24
Cho/Cr	0.50	0.10	24
MIno/Cr	0.37	0.09	24

*Beck Anxiety Inventory, **Beck Depression Inventory II

Table 2: Correlation between clinical symptoms of tension-type headaches (TTH) and concentrations of brain metabolites.

Variable	Trigger point count		Headache frequency		Headache intensity		*BAI		**BDI- II	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
Anterior cingulate cortex										
NAA/Cr	-0.116	0.589	0.094	0.664	0.017	0.935	-0.157	0.463	0.000	0.999
Glx/Cr	-0.126	0.557	0.025	0.907	-0.106	0.623	0.204	0.338	-0.112	0.602
Cho/Cr	-0.262	0.216	-0.109	0.611	0.057	0.791	0.200	0.348	-0.121	0.572
MIno/Cr	0.063	0.771	0.049	0.822	0.162	0.450	0.021	0.922	-0.081	0.708
Thalamus										
NAA/Cr	-0.192	0.369	-0.033	0.879	0.004	0.985	-0.294	0.164	-0.096	0.656
Glx/Cr	-0.028	0.898	0.181	0.396	0.209	0.326	0.267	0.207	0.218	0.306
Cho/Cr	-0.139	0.517	0.031	0.886	0.153	0.474	0.209	0.327	0.120	0.578
MIno/Cr	-0.348	0.096	0.147	0.492	0.053	0.804	0.040	0.853	0.008	0.971
Primary somatosensory cortex										
NAA/Cr	0.065	0.762	0.270	0.203	0.075	0.727	-0.167	0.435	-0.308	0.143
Glx/Cr	-0.197	0.356	0.064	0.768	-0.058	0.788	0.096	0.655	0.007	0.976
Cho/Cr	-0.509	***0.011	-0.013	0.950	0.139	0.516	0.197	0.355	0.163	0.447
MIno/Cr	-0.246	0.247	0.220	0.301	0.249	0.241	0.149	0.487	-0.026	0.904

*Beck Anxiety Inventory, **Beck Depression Inventory II, ***indicates significant difference at< 0.05

Discussion

Our results showed a negative correlation between trigger point count and Cho/Cr ratio in the primary somatosensory cortex. Other clinical symptoms of TTH, including headache frequency and intensity, anxiety and depression were not associated with metabolite levels. These results are consistent with findings published by Petrou et al., in 2008. These authors showed that there were no correlations between anxiety, depression or pain catastrophizing scale score and metabolite concentrations in patients with fibromyalgia; however, they found that Cho/Cr ratio was positively correlated with the patients' pain level [16].

Choline concentration may reflect cellular attenuation, membrane synthesis, and/or cell numbers in brain tissue. Changes in Cho/Cr ratio may indicate altered brain metabolism. Hyper-osmotic or hypo-osmotic conditions may also be reflected by choline alterations. Furthermore, choline is the precursor of acetylcholine [1, 16, 17]. Nociceptive inputs from trigger points may affect brain metabolism, osmotic condition and/or the amount of acetylcholine in the brain. In the present study, lower Cho/Cr ratios were associated with higher numbers of trigger points. This association suggests that the incidence or existence of trigger points is related to changes in brain metabolic activity. It can be hypothesized that the transformation of choline to acetylcholine influences the development of trigger points. Considering that acetylcholine modulates synaptic transmission and increases the signal to noise ratio in the cortex by suppressing inputs from environmental stimuli that do not need an immediate reaction, it is plausible that cho-

line conversion to acetylcholine is a mechanism over riding the prolonged nociceptive inputs from trigger points to the central nervous system [18]. Besides, confirmation of this hypothesis needs further study.

It has been suggested that alterations in brain metabolites are involved in the pathogenesis of mood disorders such as anxiety and depression [19-22]. In patients with depression, blood flow and neuronal energy consumption are reduced, and neurotransmitter systems in the brain altered [19]. The role of altered glutamate activity in the pathophysiology of depression was recently confirmed [23]. In patients with anxiety, changes in brain function and structure as well as metabolic abnormalities are known to occur [24, 25].In this connection, Harper et al. found a correlation between choline concentration and negative mood in patients with chronic pelvic pain syndrome [26]. Unique advantages of ^{1}HMRS are the ability to provide important quantitative biochemical information in localized brain areas, and to document brain metabolic activity efficiently in people with mood disorders [19, 25]. In addition, an association has been reported between chronic headaches and central nervous system alterations [11]. The lack of correlation between headache characteristics and patients' mood in the present study may be ascribed to the mild level of mood disorders in our participants. Moreover, investigating larger samples and populations may yield different results.

In this study, we investigated only the left hemisphere of the brain because of the high cost of MRS. Assessments in both hemispheres and other brain centers hold the potential to provide more information in future study.

Conclusion

In patients with TTH, the number of trigger points in cervical muscles correlated negatively with Cho/Cr ratio in the primary somatosensory cortex and patients with more trigger points had lower Cho/Cr ratios. However, there were no correlations between other brain metabolite concentrations and headache frequency, headache intensity, anxiety or depression.

Acknowledgment

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Conflict of Interest

None

References

1. Panigrahy A, Nelson Jr MD, Blueml S. Magnetic resonance spectroscopy in pediatric neuroradiology: clinical and research applications. *Pediatr Radiol.* 2010;**40**:3-30. doi: 10.1007/s00247-009-1450-z. PubMed PMID: 19937238.
2. Chang L, Munsaka SM, Kraft-Terry S, Ernst T. Magnetic resonance spectroscopy to assess neuroinflammation and neuropathic pain. *J Neuroimmune Pharmacol.* 2013;**8**:576-93. doi: 10.1007/s11481-013-9460-x. PubMed PMID: 23666436. PubMed PMCID: PMC3698315.
3. Van Der Graaf M. In vivo magnetic resonance spectroscopy: basic methodology and clinical applications. *Eur Biophys J.* 2010;**39**:527-40. doi: 10.1007/s00249-009-0517-y. PubMed PMID: 19680645. PubMed PMCID: PMC2841275.
4. Jansen JF, Backes WH, Nicolay K, Kooi ME. 1H MR spectroscopy of the brain: absolute quantification of metabolites. *Radiology.* 2006;**240**:318-32. doi: 10.1148/radiol.2402050314. PubMed PMID: 16864664.
5. Tracey I. Can neuroimaging studies identify pain endophenotypes in humans? *Nat Rev Neurol.* 2011;**7**:173-81. doi: 10.1038/nrneurol.2011.4. PubMed PMID: 21304481.
6. Grachev ID, Fredrickson BE, Apkarian AV. Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study. *Pain.* 2000;**89**:7-18. doi: 10.1016/s0304-3959(00)00340-7. PubMed PMID: 11113288.
7. Zhao X, Xu M, Jorgenson K, Kong J. Neurochemical changes in patients with chronic low back pain detected by proton magnetic resonance spectroscopy:

A systematic review. *Neuroimage Clin.* 2017;**13**:33-8. doi: 10.1016/j.nicl.2016.11.006. PubMed PMID: 27920977. PubMed PMCID: PMC5126149.

8. Grachev ID, Thomas PS, Ramachandran TS. Decreased levels of N-acetylaspartate in dorsolateral prefrontal cortex in a case of intractable severe sympathetically mediated chronic pain (complex regional pain syndrome, type I). *Brain Cogn.* 2002;**49**:102-13. doi: 10.1006/brcg.2001.1489.
9. Pattany PM, Yezierski RP, Widerstrom-Noga EG, Bowen BC, Martinez-Arizala A, Garcia BR, et al. Proton magnetic resonance spectroscopy of the thalamus in patients with chronic neuropathic pain after spinal cord injury. *AJNR Am J Neuroradiol.* 2002;**23**:901-5. PubMed PMID: 12063213.
10. Siddall PJ, Stanwell P, Woodhouse A, Somorjai RL, Dolenko B, Nikulin A, et al. Magnetic resonance spectroscopy detects biochemical changes in the brain associated with chronic low back pain: a preliminary report. *Anesth Analg.* 2006;**102**:1164-8. doi: 10.1213/01.ane.0000198333.22687.a6. PubMed PMID: 16551917.
11. Lai TH, Protsenko E, Cheng YC, Loggia ML, Coppola G, Chen WT. Neural Plasticity in Common Forms of Chronic Headaches. *Neural Plast.* 2015;**2015**:205985. doi: 10.1155/2015/205985. PubMed PMID: 26366304. PubMed PMCID: PMC4558449.
12. Jensen R, Stovner LJ. Epidemiology and comorbidity of headache. *The Lancet Neurology.* 2008;**7**:354-61.
13. Dadfar M, Kalibatseva Z. Psychometric Properties of the Persian Version of the Short Beck Depression Inventory with Iranian Psychiatric Outpatients. *Scientifica (Cairo).* 2016;**2016**:8196463. doi: 10.1155/2016/8196463. PubMed PMID: 27293979. PubMed PMCID: PMC4886104.
14. Khesht-Masjedi MF, Omar Z, Masoleh SMK. Psychometrics properties of the Persian version of Beck Anxiety Inventory in North of Iranian adolescents. *International Journal of Educational and Psychological Researches.* 2015;**1**:145. doi: 10.4103/2395-2296.152233.
15. Gussew A, Rzanny R, Gullmar D, Scholle HC, Reichenbach JR. 1H-MR spectroscopic detection of metabolic changes in pain processing brain regions in the presence of non-specific chronic low back pain. *Neuroimage.* 2011;**54**:1315-23. doi: 10.1016/j.neuroimage.2010.09.039. PubMed PMID: 20869447.
16. Petrou M, Harris RE, Foerster BR, McLean SA, Sen A, Clauw DJ, et al. Proton MR spectroscopy in the evaluation of cerebral metabolism in patients with fibromyalgia: comparison with healthy controls and correlation with symptom severity. *AJNR Am J Neuroradiol.* 2008;**29**:913-8. doi: 10.3174/ajnr.A0959. PubMed PMID: 18339723.
17. Castillo M, Kwock L, Mukherji SK. Clinical applications of proton MR spectroscopy. *AJNR Am J Neuroradiol.* 1996;**17**:1-15. PubMed PMID: 8770242.
18. Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. *Neuron.* 2012;**76**:116-29. doi: 10.1016/j.neuron.2012.08.036. PubMed PMID: 23040810. PubMed PMCID: PMC3466476.
19. Auer DP, Putz B, Kraft E, Lipinski B, Schill J, Holsboer F. Reduced glutamate in the anterior cingulate cortex in depression: an in vivo proton magnetic resonance spectroscopy study. *Biol Psychiatry.* 2000;**47**:305-13. doi: 10.1016/s0006-3223(99)00159-6. PubMed PMID: 10686265.
20. Moon C-M, Jeong G-W. Brain morphological alterations and cellular metabolic changes in patients with generalized anxiety disorder: a combined DARTEL-based VBM and 1 H-MRS study. *Magn Reson Imaging.* 2016;**34**:429-36. doi: 10.1016/j.mri.2015.12.017.
21. Li Y, Jakary A, Gillung E, Eisendrath S, Nelson SJ, Mukherjee P, et al. Evaluating metabolites in patients with major depressive disorder who received mindfulness-based cognitive therapy and healthy controls using short echo MRSI at 7 Tesla. *Magnetic Resonance Materials in Physics, Biology and Medicine.* 2016;**29**:523-33. doi: 10.1007/s10334-016-0526-7.
22. As-Sanie S, Kim J, Schmidt-Wilcke T, Sundgren PC, Clauw DJ, Napadow V, et al. Functional connectivity is associated with altered brain chemistry in women with endometriosis-associated chronic pelvic pain. *The Journal of Pain.* 2016;**17**:1-13. doi: 10.1016/j.jpain.2015.09.008.
23. Godlewska BR, Masaki C, Sharpley AL, Cowen PJ, Emir UE. Brain glutamate in medication-free depressed patients: a proton MRS study at 7 Tesla. *Psychol Med.* 2018;**48**:1731-7.
24. Moon CM, Kang HK, Jeong GW. Metabolic change in the right dorsolateral prefrontal cortex and its correlation with symptom severity in patients with generalized anxiety disorder: Proton magnetic resonance spectroscopy at 3 T esla. *Psychiatry Clin Neurosci.* 2015;**69**:422-30.
25. Delvecchio G, Stanley JA, Altamura AC, Brambilla P. Metabolic alterations in generalised anxiety disorder: a review of proton magnetic resonance spectroscopic studies. *Epidemiol Psychiatr Sci.* 2017;**26**:587-95. doi: 10.1017/S2045796017000361. PubMed PMID: 28789715.
26. Harper DE, Ichesco E, Schrepf A, Halvorson M, Puiu T, Clauw DJ, et al. Relationships between brain metabolite levels, functional connectivity, and negative mood in urologic chronic pelvic pain syndrome patients compared to controls: A MAPP research network study. *Neuroimage Clin.* 2018;**17**:570-8. doi: 10.1016/j.nicl.2017.11.014. PubMed PMID: 29201643. PubMed PMCID: PMC5702874.