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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

KRANİYAL LEZYONLARIN AYIRICI TANISINDA MAGNETİK REZONANS SPEKTROSKOPİNİN ÖNEMİ VE PATOLOJİ SONUÇLARI İLE KORELASYONU

THE IMPORTANCE OF MAGNETIC RESONANCE SPECTROSCOPY IN THE DIFFERENTIAL DIAGNOSIS OF CRANIAL LESIONS AND ITS CORRELATION WITH PATHOLOGY RESULTS

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ÖZET

AMAÇ: Kraniyal lezyonlarda tedavi algoritmasının belirlenmesinde operasyon öncesi tanı çok önemlidir. Bu çalışma ile preoperatif yapılan görüntüleme yöntemlerinden magnetik rezonans spektroskopi sonuçlarının patoloji sonuçları ile karşılaştırılması ile tanı koymadaki etkinliğinin ortaya konulması amaçlanmıştır.

GEREÇ VE YÖNTEM: 2016 - 2019 yılları arasında kliniğimizde kranial yer kaplayıcı lezyon nedeniyle opere edilen 75 hasta içerisinden operasyon öncesi magnetik rezonans spektroskopi görüntülemesi yapılan 35 hasta çalışmaya alındı. Biyokimyasal metabolit olarak N-asetil aspartat, kreatin, kolin ve laktat değerleri hesaplandı ve bu değerlere göre konulan preoperatif tanılar postoperatif patoloji sonuçları ile karşılaştırılarak literatür eşliğinde tartışıldı.

BULGULAR: Çalışmaya 20 erkek, 15 kadın toplam 35 hasta dahil edildi. Hastaların yaş aralığı 18 - 82 arasında idi. Magnetik rezonans spektroskopi sonucunda 29 hastada yüksek gradeli glial tümör tanısı kondu. Operasyon sonrası değerlendirme sonucunda 27 hastanın magnetik rezonans spektroskopi sonucu ile patoloji sonuçları uyumlu bulunurken 8 hastada farklılıklar görüldü. Yüksek gradeli glial tümörlerde kolin piki ve kolin/NAA oranında belirgin artma dikkat çekti.

SONUÇ: Kraniyal lezyonların ayırıcı tanısında yapılan magnetik rezonans spektroskopi ile elde edilen preoperatif değerlendirmeler ile patolojik tanı arasında yüksek oranda korelasyon mevcutdur.

ANAHTAR KELİMELER: Tümör, Spektroskopi, Cerrahi, Patoloji

ABSTRACT

OBJECTIVE: Preoperative diagnosis is very important in determining the treatment algorithm in cranial lesions. The aim of this study is to compare the results of magnetic resonance spectroscopy, which is one of the preoperative imaging methods, with the results of pathology and to reveal its effectiveness in diagnosis.

MATERIAL AND METHODS: Thirty five patients who underwent preoperative magnetic resonance spectroscopy imaging among 75 patients who were operated for cranial lesions in our clinic between 2016 - 2019 were included in the study. N-acetyl aspartate, creatine, choline and lactate values were calculated as biochemical metabolites, and preoperative diagnoses made according to these values were compared with postoperative pathology results and discussed in the light of the literature.

RESULTS: A total of 35 patients, 20 male and 15 female, were included in the study. The age range of the patients was between 18 - 82. As a result of magnetic resonance spectroscopy, 29 patients were diagnosed with high grade glial tumors. As a result of the postoperative evaluation, the magnetic resonance spectroscopy results of 27 patients were found to be compatible with the pathology results, while differences were observed in 8 patients. A significant increase in choline peak and choline / NAA ratio was noted in high-grade glial tumors.

CONCLUSIONS: There is a high correlation between the preoperative evaluations obtained by magnetic resonance spectroscopy which is used in the differential diagnosis of cranial lesions, and the pathological diagnosis.

KEYWORDS: Tumor, Spectroscopy, Surgery, Pathology

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INTRODUCTION

The definition of cranial space-occupying lesions includes many different disease groups. Differential diagnosis of these diseases is very important. Especially the differentiation of tumor-like lesions that can be confused with neoplasms has very important results in terms of treatment and survival. The success of postoperative radiotherapy or chemotherapy directly affects the size of the excised tumor. Clarifying the preoperative diagnosis is of great importance in surgical planning.

Magnetic resonance imaging (MRI) is the first imaging method used in the differential diagnosis of cranial lesions. Magnetic resonance spectroscopy (MRS) has become available after the use of MRI (1). The basic principle of MRS is that it gives results through tissue biochemistry and metabolism. MRS was first used in the clinic in 1960. It can be applied using single voxel or multivococcal imaging techniques (2). Correct placement of the voxel is important. Multiple regions can be evaluated simultaneously with multivoxel, larger volumes can be studied; however, the examination takes longer. In voxel selection, measurement should be made from the place where the pathology is most obvious. As the voxel value increases, the amount of tissue and signal it contains also increases.

The pathological tissue entering into the voxel should be increased as much as possible and the normal brain tissue surrounding the lesion should be less (3).

In this study, it was aimed to demonstrate the specificity and diagnostic success of MRS used in imaging cranial lesions by comparing the diagnoses obtained by evaluating the peaks of metabolites in the proton MRI spectrum obtained from abnormal brain tissues and the pathology results obtained after the operation.

MATERIAL AND METHOD

Among the 75 patients diagnosed with cranial lesions in our clinic between 2016 and 2019, 35 patients who had preoperative MRS imaging were included in the study. Patients who were diagnosed for the first time, who had not undergone previous surgery, who did not receive radiotherapy or chemotherapy and who had a single cranial lesion above the age of 18 were included in the study and patients who did not meet these criteria and those who had another known organ mass that could have metastasis were excluded. Contrast enhanced MRI and MRS were performed in all patients before the operation. A Philips brand (Philips Achieva, Philips Medical System) device was used for this shooting. Multivoxel proton spectra were obtained by MRS using 1.5 Tesla MRI.

Based on previous studies in MRS, it was decided to study N-Acetyl aspartate (NAA), creatinine, choline and lactate metabolites.

Peak intensities and areas on normal and pathological brain tissues were measured on the obtained spectra. NAA, creatinine, choline and lactate values obtained from pathological regions were compared with NAA, creatinine, choline and lactate values obtained from normal brain parenchyma and their ratios were determined. In the light of these rates, the diagnoses reported in the postoperative pathology reports were compared.

Ethical Committee

This study was conducted after the approval of Afyonkarahisar Health Sciences University Ethics Committee (05.06.2020, 2020/243).

RESULTS

Of the 35 cases evaluated in the study, 20 cases were male and 15 cases were female. The age range of the cases was 18 - 82 (mean: 56.12). The lesion was on the right in 19 patients. As a result of MRS measurements, 25 cases were diagnosed with high-grade glial tumor, 5 cases with low-grade glial tumor, 2 cases with oligodendroglioma, 1 case with hematoma, 1 case with metastasis, and 1 case with lymphoma. Pathology diagnosis was made by open surgery or stereotaxic biopsy. According to the pathology reports, 23 cases were diagnosed with high-grade glial tumor, 3 cases with low-grade glial tumor, 3 cases with oligodendroglioma, 2 cases with metastasis, 2 cases of hemorrhage, 1 case of lymphoma and 1 case of granulomatous disease **(Table 1)**.

Table 1: General Characteristics Of The Patients

NO	AGE	GENDER	MRS RESULT	PATHOLOGY RESULT
1	75	M	HIGH GRADE	GBM WHO GRADE 4/4
2	40	M	CHO↑ NAA↓ CHO/CR ↑ CHO/NAA ↑ HIGH GRADE	GBM WHO GRADE 4/4
3	68	M	CHO/NAA >1.2 HIGH GRADE	GBM WHO GRADE 4/4
4	74	F	CHO↑NAA↓, NAA/CR <1.6, NAA/CHO<1.2 OLİGODENDROGLİOM	OLIGODENDROGLIOM GRADE 2
5	62	F	CHO/NAA >2.11 HIGH GRADE	GBM WHO GRADE 4/4
6	60	F	CHO/NAA >3 HIGH GRADE	GBM WHO GRADE 4/4
7	56	F	CHO/CR ↑ NAA/CR ↓ HIGH GRADE	OLİGODENDROGLİOM GRADE 2/3
8	35	M	CHO: 3.43,CR:1.21,NAA:2,04, CHO/NAA:1.68 HIGH GRADE	GBM WHO GRADE 4/4
9	18	F	CHO/NAA: N, INOSITOL ↑, LAC ↑, CORTICAL DYSPLASIA	CORTICAL DYSPLASIA
10	82	M	CHO/CR: 2-2.5 LIPIT ↑LAC ↑ HIGH GRADE	GBM WHO GRADE 4/4
11	73	M	CHO ↑, CHO/NAA>1. HIGH GRADE	GBM WHO GRADE 4/4
12	77	M	CHO/NAA >1.5 LOW GRADE	HEMATOMA
13	46	F	CHO/NAA:7, CHO/CR:3.5 HIGH GRADE	GRANULOMATOUS DİSEASE TUBERCULOSIS
14	33	F	LIPIT↑ LAC ↑LOW GRADE	LOW GRADE. DIF. ASTROSITOM GRADE 2/4
15	55	M	LOW GRADE	GBM WHO GRADE 4/4
16	18	M	CHO/NAA >1.5 LOW GRADE	LOW GRADE
17	58	M	NAA ↓, CHO: N. LIPIT ↑, LAC ↑, LOW GRADE	HEMATOMA
18	66	F	CHO/NAA >1.5 ,NAA ↓. HIGH GRADE	GBM WHO GRADE 4/4
19	53	M	CHO/NAA :4.6 LYMPHOMA	GBM WHO GRADE 4/4
20	73	M	CHO ↑. CHO/NAA>1.5 HIGH GRADE	GBM WHO GRADE 4/4
21	56	F	CHO/NAA 16, CHO/CR >1.2 HIGH GRADE	GBM WHO GRADE 4/4
22	64	M	CHO/CR 11, CHO/NAA 15 HIGH GRADE	GBM WHO GRADE 4/4
23	72	F	CHO/NAA 1.2 ↑HIGH GRADE	LYMPHOMA
24	66	F	CHO: ↑, CHO/NAA: ↑, CHO/CR ↑. HIGH GRADE	ADENOCARSINOMA
25	26	M	NAA/CR<1.6, NAA/CHO<1.2, CHO/CRE: 1.53 . LOW GRADE	DIF ASTROSITOM GRADE 2/4
26	24	M	CHO ↑, NAA ↓, CHO/CR ↑, NAA/CR: ↓, HIGH GRADE	GBM WHO GRADE 4/4 ASTROSITOM GRADE 2
27	31	M	CHO/CR: 5.4, CHO/ NAA 5.56 HIGH GRADE	
28	60	M	CHO/CR: 6.5, CHO/ NAA 0.5 METASTASIS	ADENOCARSINOMA
29	68	F	CHO/NAA>1.2. HIGH GRADE	GBM WHO GRADE 4/4
30	62	F	CHO/CR: ↑, CHO/NAA: ↑. HIGH GRADE	GBM WHO GRADE 4/4
31	67	M	HIGH GRADE	GBM WHO GRADE 4/4
32	80	F	CHO↑, NAA ↓, CHO/CR: ↑, CHO/NAA: ↑, HIGH GRADE	GBM WHO GRADE 4/4
33	75	F	CHO/NAA >1.2 HIGH GRADE	GBM WHO GRADE 4/4
34	40	F	CHO↑, NAA ↓, NAA/CR <1.6, NAA/CHO<1.2 OLİGODENDROGLİOM	GBM WHO GRADE 4/4
35	68	F	CHO/NAA: 2.11, HIGH GRADE	GBM WHO GRADE 4/4

In 22 of 25 cases diagnosed with high grade glial tumor after MRS, the pathology result was compatible with the diagnosis. Choline peak and NAA decrease were observed in all 22 cases **(Figure 1)**.

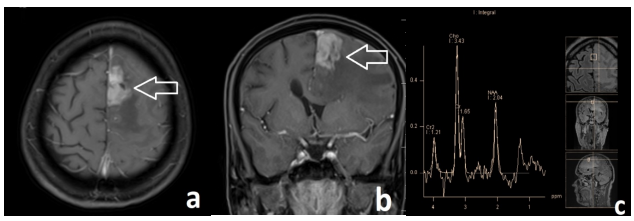

Figure 1: 35 years old male patient.
a. Intraaxial lesion in the left frontal lobe at the level of the superior and middle frontal gyri. MRI axial section T2AG image.
b. MRI Coronal section T2AG image
c. Peak waves of metabolites measured after MRS.

The mean choline / NAA was found to be> 3. Other cases were reported as oligodendroglioma, granulomatous disease and lymphoma. The mean peak levels obtained from the lesion area were measured as NAA: 1.56, creatinine: 1.84 and choline: 4.2. Choline / NAA: 2.68, choline / creatinine: 2.28 and creatinine / NAA: 1.17. While a significant decrease was observed in NAA levels due to neuronal loss in these regions, a moderate decrease was observed in creatinine levels. The increase in choline values was measured. Mean peak levels of these cases were found to be NAA: 4.26, choline: 2.42, creatinine: 2.24, choline / NAA: 0.56, choline / creatinine: 1.08, and creatinine / NAA: 0.52 in the analysis of normal-appearing brain parenchyma.

Choline: 2.24, creatinine: 0.62 and NAA: 0.31 were measured in MRS in one patient. An approximately seven-fold increase in the choline / NAA ratio was found, and the patient was reported as a high grade glial tumor. Postoperative pathology result was reported as granulomatous disease (Tuberculosis) **(Figure 2)**.

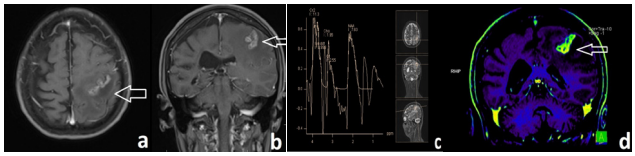

Figure 2: 46-year-old female patient.
a. MRI axial section view of the lesion with vasogenic edema around the parietal lobe postcentral gyrus with heterogeneous irregular contrast enhancement
b. MRI Coronal section T2AG image
c. Peak waves of metabolites measured after MRS
d. Lesion image taken after MRP.

Although there was no choline peak in one patient, it was stated that there might be a low-grade glial tumor due to decreased NAA, lipid and lactate peak, and the pathology result of the patient was hematoma. During the follow-up, no lesion suggesting a tumor was observed in the control MRI. In another case, high-grade glial tumor was considered due to choline / NAA> 1.2, and the pathology result was reported as lymphoma. In the examination of MRS in 2 cases with pathology results, choline peak was observed in 1 case and choline / NAA and choline / Creatinine ratios were increased, while the choline / NAA ratio was low in the other case.When the postoperative pathological diagnoses were compared with MRS, it was found that 77% (27 of 35 patients were compatible).

DISCUSSION

When faced with a cranial space-occupying lesion, the first thing to do is to make the preoperative diagnosis as accurately as possible in terms of treatment planning. Especially the differentiation of tumor-like lesions that can be confused with neoplasms has very important results in terms of treatment and survival. Preoperative comprehensive imaging is one of the

factors affecting diagnosis and success. Imaging enables staging, formulating preoperative strategies, monitoring treatment response, and obtaining information critical to postoperative surveillance and prognosis (4). Therefore, imaging methods form the basis of preoperative planning, postoperative evaluation, radiotherapy planning and post-treatment surveillance (2).

MRI is the first imaging method used in the differential diagnosis of cranial lesions. In recent years; Magnetic resonance perfusion (MRP) imaging, which provides information about tissue microcirculation, MRS, which provides information about tissue biochemistry and metabolism, and diffusion imaging of microscopic water movement have been developed (5). MRP imaging is much more successful and reliable in showing pseudoprogression (6). The combination of MRI and positron emission tomography (PET) is important both in the initial treatment planning and in treatment planning after recurrence (7). Increased cell density in malignant brain tumors leads to the restriction of water disivity and lower Apparent Diffusion Coefficient (ADC) signal values (8).

MRS is a non-invasive diagnostic method that monitors metabolic changes in brain tumors (9, 10). Although a tumor-specific metabolite has not been identified to date, some markers have been identified for tumor characterization. These are NAA showing neuronal integrity, choline, a cell membrane synthesis marker, creatinine, a bioenergy storage marker, and lactate, a product of anaerobic glycolysis (11).

Although the incidence of central nervous system tumors is between 10-17 per 100,000 on average, 9% of tumor-related deaths are caused by tumors of this system. Cerebral gliomas in this group constitute approximately 24% of primary brain tumors with a worldwide case incidence rate. Meningiomas are the second most common intracranial tumors in the adult group, and these two groups constitute an important part of all cancer morbidity and mortality (12).

In brain tumors, generally decreased NAA, increased choline and again decreased creatinine signal are detected. Similar results were obtained in the study conducted by Esen et al. (13). In our study, the mean peak levels obtained from the tumoral region were NAA: 1.56, creatinine: 1.84 and choline: 4.2, choline / NAA: 2.68, choline / creatinine: 2.28 and creatinine / NAA: 1.17. While a significant decrease was observed in NAA levels due to neuronal loss in these regions, a moderate decrease was observed in creatinine levels. The increase in choline values was measured. The mean peak levels of these cases in the analysis performed from normal appearing brain parenchyma were NAA: 4.26, choline: 2.42, creatinine: 2.24, choline / NAA: 0.56, choline / creatinine: 1.08 and creatinine / NAA: 0.52. The choline / NAA ratio may not always be increased in gliomas. This is because gliomas have different metabolic properties (14). In our study, 23 patients were reported as high-grade glial tumors as a result of preoperative MRS, and decreased NAA, increased choline and decreased creatinine levels were measured in all of these patients. Postoperative pathology reports showed that 2 patients had low grade astrocytoma, one patient had lung metastasis, and one patient had granulomatous disease. Although it was reported that there was no choline peak in one patient, the choline / NAA ratio was normal and the patient could have non-tumor pathologies in the preoperative MRS, the pathology result was a low-grade glial tumor.

The association of choline, whose value increases as a result of the increase in cellular membrane synthesis, and a decrease due to neuron loss, is the distinguishing feature of actively growing malignant brain neoplasms (15). As the malignancy of gliomas increases, NAA and creatinine levels decrease, while choline, lipid and lactate peaks increase. In our study, 96% of the patients with high-grade tumors (Glioblastome multiforme WHO (World Health Organization) Grade 4/4) had high choline and decreased NAA, and choline / NAA ratios were found to be 4.53 on average.

It is not easy to differentiate calcified granuloma due to tuberculosis by imaging findings. Neurocysticercosis, metastases, lymphoma, toxoplasma, glioblastoma multiforme and pyogenic abscess should be considered in the differential diagnosis. Tuberculomas include a hyperinten-

se rim in MRI, a hypointense area in the center, perilesional vasogenic edema and annular structures (16). In MRS, a decrease in NAA / creatinine, a slight decrease in NAA / choline, and an increase in lipid and lactate peaks are usually observed (17). In most recent studies, a single peak peak of 3.8 ppm is observed in the area representing lipids and glutamine in most tuberculomas, and this is absent in most malignant tumors. This peak is a sign for distinguishing lesions, but this peak is extremely difficult to measure (18). In one of our patients, choline / NAA: 7.22 and choline / creatinine: 3.61 were found and the pathology result of the patient reported as a high-grade mass was granulomatous disease, tuberculosis.

Lipid resonances become more pronounced in the presence of necrosis in cranial metastatic lesions. However, since lipid resonance can be seen in high-grade glial tumors, it is difficult to distinguish between two tumor groups with this finding only by MRS. Other imaging methods should also be used. In our study, choline peak was observed in MRS in 1 case, it was called high-grade glial tumor because choline / NAA and choline / creatinine were increased, but it was interpreted as carcinoma metastasis in the pathology report.

Choline / Creatinine ratio is used in many studies to distinguish between low-grade glial tumor and high-grade glial tumors. However, since these findings are nonspecific and may change in other lesions of the central nervous system, their use alone in the differential diagnosis may give incorrect results (19).

This study was carried out to investigate the success of imaging methods for the diagnosis of cranial lesions. The low number of cases may cause negativity. Again, the interpretation of spectroscopy reports by different radiologists may cause negativity.

It should be kept in mind that MRS alone may not be used in the differential diagnosis of cranial space-occupying lesions, and it is seen that highly accurate results can be obtained when it is used together with MRI and other advanced examination methods in the evaluation of brain tumors, differentiation and staging from other non-tumoral lesions.

REFERENCES

1. Fink JR, Muzi M, Peck M, Krohn KA. Continuing education: Multimodality brain tumor imaging - MRI, PET, and PET / MRI. J Nucl Med. 2015;56:1554-61.

2. Warren KE. NMR spectroscopy and pediatric brain tumors. Oncologist. 2004;9(3):312-18.

3. Tosun A, Serifoglu I. Imaging of Central Nervous System Tumors. Acta Med Alanya. 2018;2(1):56-61.

4. Najjar AM, Johnson JM, Schellingerhout D. The emerging role of amino acid PET in neuro-oncolgy. Bioengineering (Basel). 2018;5(4):104.

5. Aksoy FG, Yerli H. Dynamic contrast brain perfusion imaging: technical principles, pitfalls and problems. Journal of diagnostic and interventional radiology. 2003;9:309-14.

6. Patel P, Baradaran H, Delgado D, et al. MR perfusion-weighted imaging in the evaluation of high-grade gliomas after treatment: a systematic review and meta-analysis. Neuro Oncol. 2017;9:118-27.

7. Fleischmann DF, Unterrainer M, Corradini S, et al. Report of rst recurrent glioma patients examined with PET-MRI prior to reirradiation. PLoS One. 2019;14:e0216111.

8. Langen KJ, Galldiks N, Hattingen E, Shah NJ. Advances in neuro-oncology imaging. Nature Reviews. Neurol. 2017;13:279-89.

9. Law M, Yang S, Wang H, et al. Glioma grading: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. Am J Neuroradiol. 2003;24:1989-98.

10. Bulakbasi N, Kocaoglu M, Ors F, Tayfun C, Ucoz T. Combination of single-voxel proton MR spectroscopy and apparent diffusion coefficient calculation in the evaluation of common brain tumors. AJNR Am J Neuroradiol. 2003;24(2):225-33.

11. Howe FA, Barton SJ, Cudlip SA, et al. Metabolic proles of human brain tumors using quantitative in vivo 1H magnetic resonance spectroscopy. Magn Reson Med. 2003;49:223-32.

12. McNeill KA. Epidemiology of brain tumors. Neurol Clin. 2016;34:981-98.

13. Esen ÖS, Bozkurt M, Adıbelli ZH, et al. Diagnostic value of proton mr spectroscopy in brain tumors. Tepecik Ed Med J. 2014;24(2):93-98.

14. Mauler J, Maudsley AA, Langen KJ, et al. Spatial Relationship of Glioma Volume Derived from 18F-FET PET and Volumetric MR Spectroscopy Imaging: A Hybrid PET/MRI Study. J Nucl Med. 2018;59:603-9.

15. Kwock L, Smith JK, Castillo M et al. Clinical applications of proton MR spectroscopy in oncology. Technol Cancer Res Treat. 2002;1:17- 28.

16. Kim TK, Chang KH, Kim CJ, Goo JM, Kook MC, Han MH. Intracranial tuberculoma: comparison of MR with pathologic findings. AJNR Am J Neuroradiol. 1995;16(9):1903-8.

17. Khanna PC, Godinho S, Patkar DP, Pungaukar SA, Lawande MA. MR spectroscopy-aided differentiation: "giant" extra-axial tuberculoma masquerading as meningioma. AJNR Am J Neuroradiol. 2006;27(7):1438-40.

18. Morales H, Alfaro H, Martinot C, Fayed N, Shipley MG. MR spectroscopy of intracranial tuberculomas: A singlet peak at 3.8 ppm as potential marker to differentiate them from malignant tumors. Neuroradiol J. 2015;28(3):294–302.

19. Brunetti A, Alfano B, Soricelli A, Tedeschi E, Mainolfi C, Covelli EM. Functional characterization of brain tumors: An overviev of potential clinical value. Nuclear Medicine & Biology. 1996;23:699-715 .