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Orjinal Araştırma / Original Article

Serebral Kitlesel Lezyonların Ayırıcı Tanısında Manyetik Rezonans Spektroskopik İnceleme

Differentiation Between Neoplastic and Nonneoplastic Brain Masses Using Intermediate Echo Time MR Spectroscopy

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Abstract

Aim: The aim of this study was to evaluate the role of intermediate echo time (TE) Proton Magnetic Resonance Spectroscopy (1 H-MRS) in the differential diagnosis of neoplastic and nonneoplastic cerebral mass lesions.

Material and Method: The research was done at Cukurova University in a 1.5 Tesla whole-body MR system. In point-resolved-single volume-spectroscopy (PRESS) localization method, Probe-P pulse sequence was studied with intermediate TE (TE=144). Of 55 cases whose diagnosis was confirmed with the histopathologically or clinical and radiological follow-up, MR Spectroscopy findings were discussed.

Results: Twenty cases' definite diagnosis were neoplastic and thirty-five cases' were nonneoplastic lesions. For tumor detection in cerebral mass lesions, intermediate TE MRS was determined 100% sensitive and 91.7% specific. The positive predictive value was 86.4% and the negative one was 100%. In this study, in the neoplastic-nonneoplastic lesion differential diagnosis, NAA/Cho, NAA/Cr, Cho/Cr, and Cho/NAA ratios were evaluated and the most useful of them were found to be Cho/NAA ratio.

Conclusion: It is concluded that intermediate TE MR Spectroscopy is a reliable imaging technique for the neoplastic-nonneoplastic differential diagnosis of the cerebral mass lesions.

Keywords: Magnetic Resonance Spectroscopy, brain neoplasms, diagnosis

Öz

Amaç: Serebral kitlesel lezyonu olan hastaların optimum klinik yönetimi için doğru tanı esastır. Konvansiyonel MR morfolojiyi değerlendiren yüksek rezolüsyonlu bir tekniktir. Ancak kesin tanı vermede yetersiz kaldığı durumlarda doku biyokimyası hakkında bilgi veren MR spektroskopi gibi fonksiyonel tekniklere ihtiyaç ortaya çıkmıştır. Bu çalışmanın amacı serebral lezyonların ayırıcı tanısında MR spektroskopinin rolünü ve neoplastik-nonneoplastik lezyon ayrımında sensitivite, spesifisite ve doğruluğunu değerlendirmektir.

Gereç ve Yöntem: 1,5 Tesla cihazda PRESS lokalizasyon metodunda Probe-P puls sekansı ile orta TE (TE=144) ile çalışıldı. Tanısı patoloji veya klinik-radyolojik takip ile kesinleşmiş 55 olgudan 37'sinde tek ve 18'inde multivoksel inceleme yapıldı. 46 olguda lezyona ve 9 olguda lezyon periferine yönelik inceleme gerçekleştirildi.

Bulgular: Olguların 20'sinde kesin tanı tümöral ve 35'inde nontümöral patoloji idi. MRS serebral lezyonlarda tümörü saptamada % 100 sensitivite,% 91,7 spesifisiteye sahip bulundu. Pozitif prediktif değer % 86,4 ve negatif prediktif değer % 100 idi. Neoplastik-nonneoplastik lezyon ayrımında NAA/Cho, NAA/Cr, Cho/Cr ve Cho/NAA oranlarının değerlendirildiği bu çalışmada en kullanışlı olan Cho/NAA oranı olup Cho/Cr oranı da hassas bulundu.

Sonuç: MR Spektroskopinin serebral lezyonlarda neoplastik-nonneoplastik lezyon ayrımında güvenilir bir yöntem olduğu sonucuna varılmıştır. Elde edilen spektral verilerden tümörü seçmede en hassas olanı Cho/ NAA oranı olup kolin artışı tümör lehine önemli bir bulgudur.

Anahtar Kelimeler: MR spektroskopi, beyin neoplazmları, tanı

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INTRODUCTION

Proton MRS (1 H-MRS) is a diagnostic technique that can measure the metabolites of tissues non-invasively and show it in a spectrum. In addition to the morphological information obtained on conventional MRI, MRS provides information on the biochemistry of the sampled tissue like cellularity, energy, neuron viability, necrosis and ischemia.[1] It is clearly shown that the spectra obtained from normal brain tissue and brain tumors are different. Thus, magnetic resonance spectroscopy is increasingly used in the classification of lesions detected in the brain.[2] The aim of this study was to evaluate the role of intermediate echo time (TE) Proton Magnetic Resonance Spectroscopy (1 H-MRS) in the differential diagnosis of neoplastic and nonneoplastic cerebral mass lesions.

Different TE sequences give different spectrums. The main metabolites identified with proton MRS with TE=135-288 milliseconds include the following: N-Acetyl Aspartate (NAA, 2.02 parts per million (ppm)), Choline (Cho, 3.22 ppm), Creatine (Cr, 3.02 ppm), Lactate (Lac, 1.33 ppm) and Lipids (Lip, 1.3 and 0.9 ppm). With intermediate TE (TE=135-144 ms) doublet Lac peak inverts below the baseline and Lip peak remains above the baseline. So lipid-lactat differentiation can be made easily. At TE 270-288 ms Lac peak doesn't invert below the baseline, the same applies for short TE (TE=30 ms). Short TE demonstrates more metabolites in the spectrum in addition to those at long TE sequences, like myoinositol (Myo, 3,56 ppm) and glutamine-glutamate (Glx, 2.05-2.50 ppm). More metabolite peaks can give more information but overlapping of the peaks in the spectrum can make evaluation difficult.[1]

NAA indicates neuronal and axonal viability and density. A decrease in NAA level is observed in a wide range of disease characterized by neuronal destruction.[1,3] Because Cr is the most stable cerebral metabolite in the spectrum, it is used as an internal reference.[1] Cho is a cellular membrane turnover marker that reflects cellular proliferation. Increase in choline concentrations is detected in a large number of tumors and shows rapid proliferation in tumor cells.[1,4,5]

The spectral changes frequently observed in brain tumors are increased Cho level, increased Cho/Cr and Cho/NAA ratios; decreased or absence NAA, and lactate or lipid presence.[1-3,6,7]

MATERIAL AND METHOD

MR spectroscopy was performed on cerebral lesions of 100 cases, to none of whom a definite diagnosis was made with other imaging modalities and the definite diagnosis was necessary for clinical follow-up and treatment, between may 2004-June 2006 at the Cukurova University Faculty of Medicine. The main purpose of this retrospective study was to differentiate between tumoral and non-tumoral lesions in consecutive patients. In treated cases with central nervous system (CNS) tumor, MRS was used for the differentiation of secondary changes after radiotherapy from tumor recurrence. In the nontumoral lesion group, the second step was to make a distinction between infarct, demyelination, abscess, encephalitis, etc.

In 55 out of 100 examinations performed, pathologic or clinicalradiological follow-up confirmed the definite diagnosis. The diagnosis was confirmed by clinical and radiological followup in 41 cases and pathology in 14 cases. Here the data of 55 confirmed cases will be discussed.

Cerebral MR imaging was performed with a 1.5 Tesla wholebody MR system (GE, Signa Excite). 38 patients with single focal, 15 patients with multiple focal and 2 patients with diffuse lesions were examined. Single voxel spectroscopy (SVS) in 37 cases and multivoxel spectroscopy (Chemical Shift Imaging, CSI) in 18 cases were performed. Single voxel spectroscopy was performed in focal and small lesions. Multivoxel spectroscopic examination was performed in lesions with diffuse, large area and peripheral edema. In 46 cases, the center of lesions and in 9 cases periphery of lesions were examined spectroscopically.

The localization method used was point-resolved-single volume-spectroscopy (PRESS), the pulse sequence was probe P and was run with intermediate TE (TE=144 milliseconds). N-acetyl aspartate (NAA), Choline (Cho) and Creatine (Cr) levels and NAA/Cho, NAA/Cr, Cho/Cr and Cho/NAA ratios were evaluated in the obtained spectrum.

SPSS 14.0 was used in the analysis of the results. In the analyzes, chi-square test, ROC analysis, and T-test were performed. Sensitivity and specificity of intermediate TE MR spectroscopy in detecting the tumor in cerebral lesions were determined.

RESULTS

The 20 cases were female and 35 were male and the mean age ±SD was 39.35±19.97 (between 3 and 75 years old). The exact diagnosis of 20 cases was neoplastic (36%) and 35 were nonneoplastic (64%). In the tumor group, 14 cases were the primary tumor (**Figure 1**), 2 cases were metastasis and 4 cases were relapse/residual disease. In the nontumoral pathology group, 13 cases were infarct, 8 cases were demyelination, 3 cases were hematoma, 2 cases were encephalitis (**Figure 2**), 2 cases were posttreatment abnormality, 2 cases were vascular malformation, 1 case abscess, 1 case tuberculoma, 1 case myotonic dystrophy, 1 case arachnoid cyst, 1 case SSPE (subacute sclerosing panencephalitis).

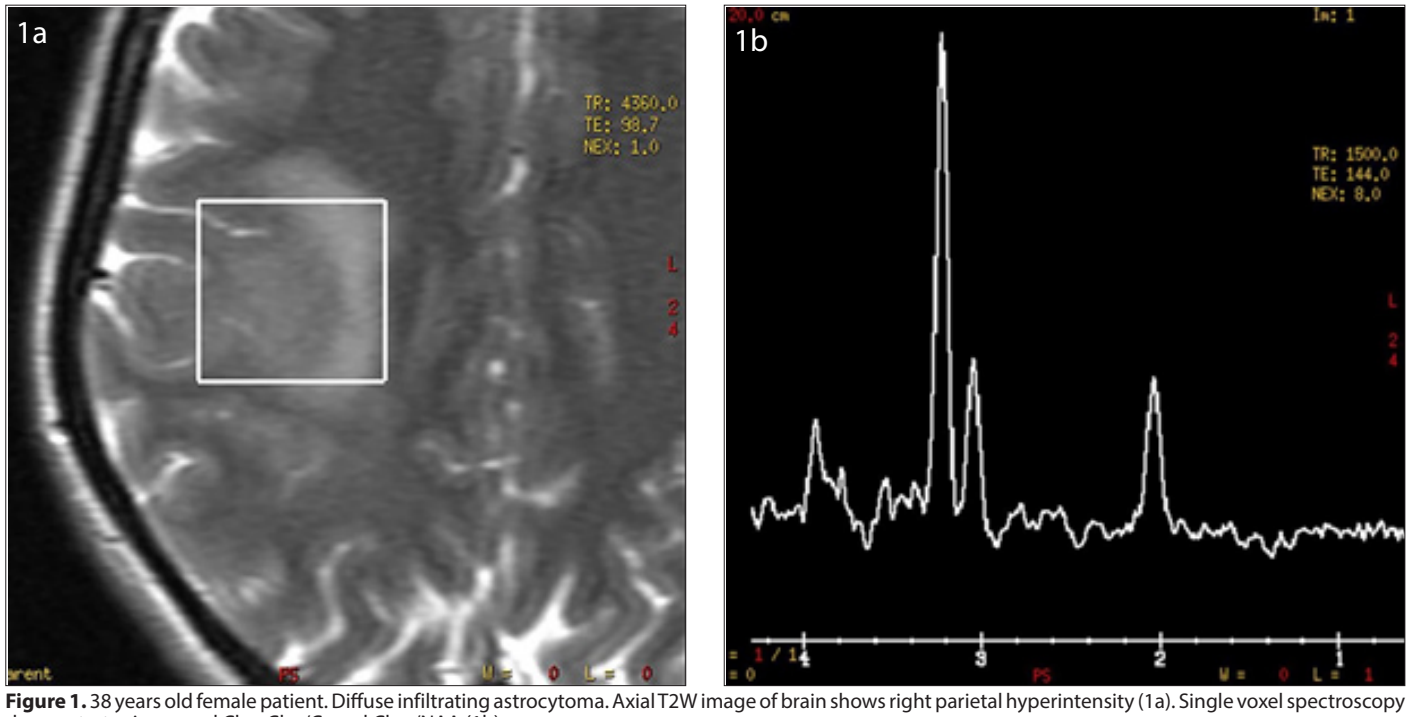

Figure 1. 38 years old female patient. Diffuse infiltrating astrocytoma. Axial T2W image of brain shows right parietal hyperintensity (1a). Single voxel spectroscopy demonstrates increased Cho, Cho/Cr and Cho /NAA (1b).

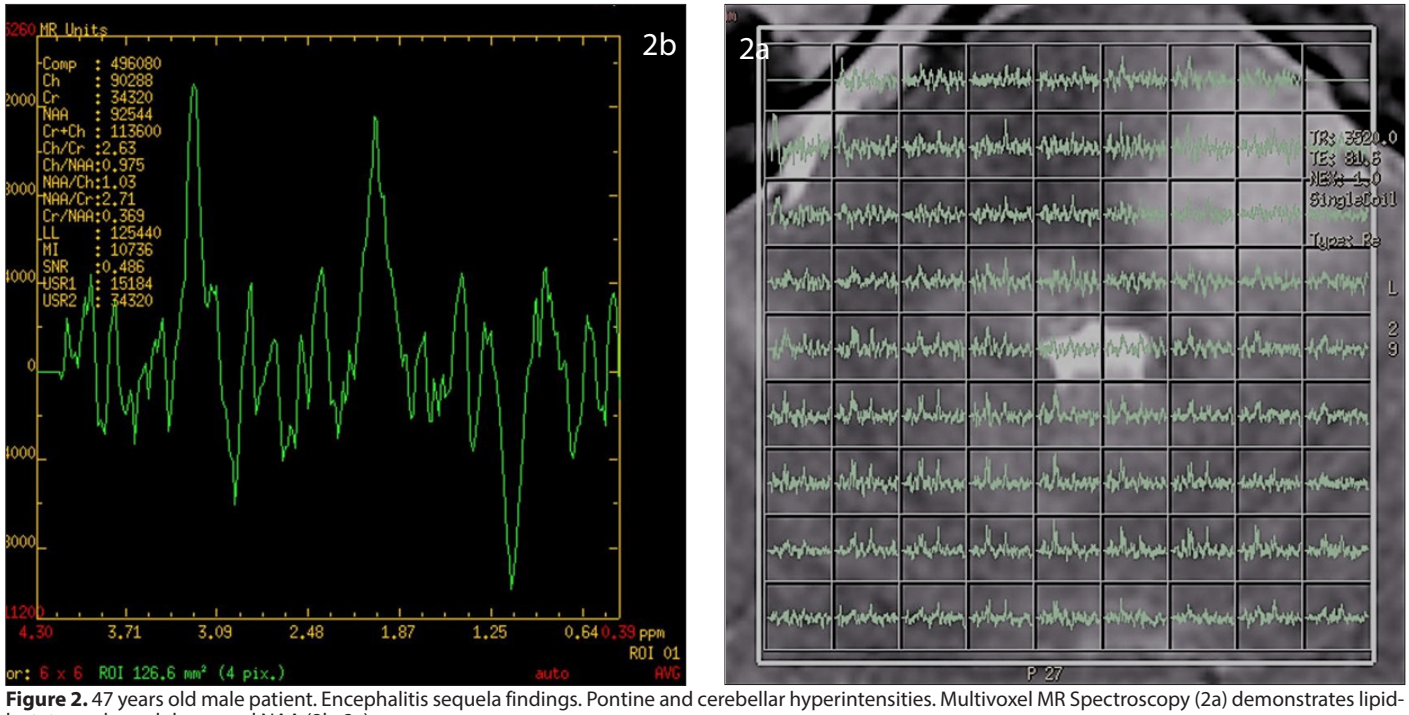

Figure 2. 47 years old male patient. Encephalitis sequela findings. Pontine and cerebellar hyperintensities. Multivoxel MR Spectroscopy (2a) demonstrates lipid-lactate peaks and decreased NAA (2b, 2c).

Intermediate TE MRS had 100% sensitivity, 91.2% specificity in detecting the tumor in cerebral lesions. The positive predictive value was 86.4% and the negative one was 100%. The mean±standard deviation of metabolite ratios in nonneoplastic and neoplastic cerebral lesions were given in **Table 1**.

Table 1. Comparison of neoplastic and nonneoplastic lesions in terms of age and metabolite ratios.

	NEOPLASTIC	NONNEOPLASTIC	P
Age	44.8±15.9	36.2±21.5	0.096
NAA/Cho	0.34±0.20	0.99±0.42	<0.001
NAA/Cr	0.88±0.42	1.38±0.44	<0.001
Cho/Cr	2.88±1.36	1.52±0.54	0.001
Cho/NAA	3.70±2.01	1.22±0.64	<0.001

When the NAA/Cho, NAA/Cr, Cho/Cr and Cho/NAA ratios were compared between tumoral and nontumoral lesions, there was a significant difference ($p < 0.05$). However, the most sensitive ratio for tumor detection was the Cho/NAA ratio and the Cho/Cr ratio was also sensitive. 8 of the 20 women (40%) were in the neoplastic and 12 (60%) were in the nonneoplastic lesion group. 27 (34.3%) of the 35 male patients were neoplastic and 23 (65.7%) were in the nonneoplastic lesion group. 40% of the females and 34.3% of the males were in the neoplastic lesion group and there was no significant difference in terms of gender ($p > 0.05$). There was no significant difference between the two groups in terms of the mean age ($p > 0.05$) (**Table 1**).

DISCUSSION

MRS is a noninvasive imaging modality that provides information about different metabolite concentrations in brain lesions. Understanding detectable metabolites and concentration changes in different pathologies play a key role in the successful use of MRS. These biochemical data, when combined with the morphological appearance of the lesion on the MRI image, provides better characterization of the lesion and increases diagnostic accuracy.[4,8-10]

Dowling et al.[11] found that abnormally increased Cho and decreased NAA indicates tumor. In the tumors, the increase in Cho is due to increased membrane synthesis in proliferating cells, the decrease in NAA is due to the destruction of neurons and axons. Generally, it was determined that Cho/NAA and Cho/Cr ratios increase as the tumor grade increases.[12] It has been reported that the level of choline is an accurate measure of evaluating the proliferative activity of the tumor.[2,5,8]

Comparison of neoplastic and nonneoplastic brain lesions in terms of metabolite ratios for our study is given in **Table 1.** A statistically significant difference was found when we compared the NAA/Cho ($p < 0.001$), NAA/Cr ($p < 0.001$), Cho/Cr ($p=0.001$) and Cho/NAA ($p < 0.001$) ratios between tumor and nontumor groups. These four ratios are useful in differentiating tumoral-nontumoral lesions and we found Cho/NAA ratio to be most useful in tumor detection.

Magalhaes et al.[12] demonstrated Cho/NAA and Cho/Cr ratios in nonneoplastic and neoplastic brain lesions. Their and our findings are consistent and given in **Table 2**. In nonneoplastic lesions, choline levels and Cho/NAA and Cho/Cr ratios are lower than neoplastic lesions and when the tumor grade increases Cho/NAA and Cho/Cr ratios increase.[8,11,12] In the study of Magalhaes et al, mean Cho/NAA ratio was slightly lower in grade 3 tumors compared to grade 2, but this may be due to the region of the sample taken. In our study, these ratios increased as the grade increased. However, if extensive necrosis is present in Grade 4 tumors, instead of an increase in these ratios, a decrease and lactate, and lipid peaks are observed.[8] In both studies, it was observed that Cho / Cr and Cho / NAA ratios continued to increase in Grade 4 tumors. This may be the result of sampling from the non-necrotic areas in grade 4 tumors. This is what needs to be done in MR spectroscopic examinations.[13]

Table 2. Comparison of metabolite ratios in astrocytomas and nonneoplastic brain lesions with Magalhaes et al's study.

	Magalhaes et al.	No (%) 25 (100)	Our findings	No (%) 44 (100)
Non tumor lesions		10 (40)		35 (80)
Cho/NAA	1.21±0.23		1.22±0.64	
Cho/Cr	1.84±0.40		1.52±0.54	
Grade 2 tumors		3 (12)		1 (2)
Cho/NAA	2.21±0.24		3.70	
Cho/Cr	1.50±0.32		2.38	
Grade 3 tumors		3 (12)		3 (7)
Cho/NAA	1.85±0.36		3.48±0.84	
Cho/Cr	1.62±0.38		2.96±1.74	
Grade 4 tumors		9 3(6)		5 (11)
Cho/NAA	6.53±1.50		5.00±2.46	
Cho/Cr	3.34±1.15		3.28±1.05	

A threshold value of 2.5 for Cho/NAA provided sensitivity and specificity were 90% and 86%, respectively, according to McKnight et al.[14] In our study, sensitivity was 73% and specificity 95% when the ratio was 2.5 or more and sensitivity was 94% and specificity 90% when the ratio was 2 or more. When the Cho/NAA ratio is increased, the sensitivity decreases but the specificity

increases.[13] In a study in which there was no statistically significant difference in metabolite ratios between different types of tumors, MRS was found to be successful in distinguishing infiltrative or limited lesions.[10]

In noninfiltrating processes such as abscesses, meningiomas, and metastases, no pathological findings were detected in spectral analyzes of nonenhanced peripheral portions.[1,15] In spectral analysis of periphery of infiltrating high-grade gliomas, it was determined that the NAA/Cho ratio is smaller than one.[10] In our study, in nine cases voxel has positioned periphery of the lesion. The NAA/Cr ratio was higher than one in the five noninfiltrating cases (two hematomas, one arachnoid cyst, one radiation necrosis, and one vascular malformation), in infiltrative four cases (two primer tumors and two tumor recurrences) it was smaller than one. Our findings are consistent with the literature.

The differentiation residual or recurrent tumor from radiation necrosis is an important application of MRS. Generally, high choline peak indicates tumor progression and low choline peak indicates radiation necrosis. Lipid peak shows necrosis that both tumor and radiotherapy can give the same appearance.[12,16] It has been reported that in tumor progression, the mean± SD values of Cho/Cr 2.30±1.29, Cho/NAA 3.44±2.76 and NAA/Cr 0.93±0.81, in radiation necrosis these values 1.26±0.61,1.29±1.17 and 1.31±0.78 respectively. Cho/Cr and Cho/NAA ratios have 82% and 81% accuracy, respectively, in differentiating neoplastic and nonneoplastic lesions. In this study, lipid-lactate values and NAA/Cr ratio were not found to be useful.[16] In our study, MRS examinations were performed in 6 cases in order to distinguish recurrent/residual tumor from radiation necrosis and we accurately detected the recurrent/ residual tumor in 4 cases and radiation necrosis in 2 cases.

It is known that TE has a significant effect on spectral data obtained in MRS. A comparative study of short to intermediate TE in discriminating between high and low-grade tumors has reported that Cho/Cr and LL/Cr ratios are useful in both TE, but short TE has a slightly higher accuracy rate.[17] In our study, we used intermediate TE (144 milliseconds) and it was reported to be ideal to assess neoplasms.[13]

In our study our priority was to make tumor-nontumor distinction. We preferred moderate TE because of less metabolite and easier evaluation option. Again, the fact that the lactate peak can be more clearly distinguished is another plus. For more specific diagnosis, short TE may be preferred. It has been reported that MRS is 95% to 100% accurate in distinguishing neoplastic and nonneoplastic lesions.[13] In our study, intermediate TE MRS had 100% sensitivity and 91.2% specificity in detecting the tumor in cerebral lesions. The positive predictive value was 86.4% and the negative predictive value was 100%.

The limitations of our study were the heterogeneity of the tumor and non-tumor groups. Another limitation is that age groups vary widely. As we could not compare between intermediate TE, short and long TE MR spectroscopy, we could not determine the advantages and disadvantages of intermediate TE MR spectroscopy.

CONCLUSION

MRS has high sensitivity, specificity and accuracy rates when it is supported by conventional MR in the differentiation of neoplastic-nonneoplastic lesions in cerebral lesions. Metabolite levels and ratios detected in intermediate TE MRS can be used to distinguish malignant and nonmalignant lesions from normal brain tissue. Cho/Cr and Cho/NAA ratios are the most sensitive values for choosing a tumor, and increase at these ratios indicate the tumor.[11-13,16] However, the obtained spectrum does not always give a specific diagnosis. Different TE sequences combination and additional other imaging methods should be used to increase the diagnostic accuracy.

ETHICAL DECLARATIONS

Ethics Comittee Approval: This study derived from Dr. Şerife Leblebisatans's medical specialty thesis in radiology (Çukurova University School of medicine, 2006/Adana, TURKEY).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Status of Peer-review: Externally peer-reviewed.

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