APPLICATION OF 1H-MRS IN GLIOMA

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ABSTRACT

Hydrogen proton spectroscopy (1H-MRS) is a non-invasive magnetic resonance imaging technique for the study of metabolism, biochemical changes and quantitative analysis of compounds in human tissues. At present, it is mainly used in the diagnosis of brain related diseases; especially, in the diagnosis, differential diagnosis, classification, defining the scope of the tumor, preoperative guidance and prognostic evaluation of glioma. This article reviews the basic principle of 1H-MRS and its clinical application in glioma.

Keywords: Glioma; Magnetic Resonance Imaging; Magnetic resonance spectroscopy.

INTRODUCTION

Gliomas are tumors originated from glial cells. They are the most common primary intracranial tumors, accounting for about 50%-60% of brain tumors, with an annual growth rate of about 1%-2% [1, 2]. At present, the annual incidence of glioma in China is (3～6.4)/100000 and the annual death toll is 30000. The incidence of malignant glioma is 5.8/100000, and the 5-year mortality rate is second only to pancreatic and lung cancers, in general [3]. Conventional MRI has been widely used in the diagnosis of glioma; and, MRS, which can reflect the biochemical and metabolic information of glioma, has drawn more and more attention. As an important auxiliary to the examination, ^{1}H-MRS can not only distinguish benign and malignant gliomas, improving the specificity of MRI diagnosis; but, can also be used to analyze the extent of tumor invasion and evaluate the therapeutic effect of the tumor [4, 5]. At present, ^{1}H-MRS has been recommended, as a specific adjuvant method, in the differential diagnosis and treatment evaluation, of benign and malignant gliomas.

MRS concept and imaging principle:

MRS is a method for quantitative analysis of specific nuclei and their compounds by using magnetic resonance phenomenon and chemical displacement. The basic principle of MRS imaging is basically the same as that of MRI; wherein, Conventional MRI forms a distribution map according to the spatial position of magnetic resonance signals; while, MRS displays many signals in a space through different peak curves, which are mainly based upon two physical phenomena: chemical displacement and J-coupling [3]. The chemical shift is caused by the effect of an external magnetic field and the density of the electron cloud around the various hydrogen nuclei, which varies in structure and position, resulting in the differentiation of resonance frequency. That is, the shift of resonance absorption peak, which causes the change of local magnetic field of atomic nuclei, and the interaction of the same atomic spin magnetic moment, in different compounds in the same uniform magnetic field, results in the formation of MRS map. The spectra are composed of multiple resonance peaks generated by nuclei, with different resonance frequencies. As the chemical shifts of the nuclei in different compounds are different, we can distinguish them according to their resonance peak frequency in MRS. In MRS, the abscissa represents the chemical shift, the ordinate represents the signal strength of the metabolites, and the area under the wave peak represents the concentration of the metabolites.

MRS imaging of the brain and it's influencing factors:

1. Biological basis of the change of metabolites in glioma:

Brain glioma is originated from glial cells. Currently, it is found that N-acetyl-aspartic acid (NAA) only exists in the nervous system and is produced by the mitochondrial cells of the neurons, which is a sign of neuron density and activity. During the development of the tumor, a large number of mitochondria of the glial cells will be destroyed, resulting in a significant decrease of NAA. Choline is involved in the synthesis and degradation of the cell membrane; which is closely related to the phospholipid metabolism of the cell membrane. Therefore, an increase of CHO indicates an accelerated synthesis of the cell membrane, with high cellular density; and, as faster the tumor cells proliferates, an increment in CHO will be more obvious. Creatinine (Cr), stored in neurons and glial cells, acts as a buffer between ATP and ADP, by storing high energy phosphate bonds, in brain cells.

Under different metabolic conditions, within the same tissue, the total amount of Cr is relatively constant, so it is often used as the reference ratio, in the spectrum. Glioma derives energy through glucose metabolism; the higher the malignant degree of the tumor, the faster is its growth, with an increase in the energy consumption; when it no longer meets the growth of the tumor, there will be anaerobic glycolysis, which can generate a large number of cellular metabolites, such as lactic acids (Lac), lipids (Lip) and other compounds. Levels of Lac and Lip, varies greatly in different grades of glioma, and often occurs in the centre of the necrotic tissues, in high grade glioma.

2. ¹H-MRS imaging of glioma:

Hydrogen proton magnetic resonance spectroscopy includes two types of imaging techniques: STEAM (stimulated echo acquisition mode) and PRESS (point resolved spectroscopy). The excitation echo sequence has a short TE time (20-30ms) and it is better to observe the Short T2 metabolites; but, the signal-to-noise ratio is low and sensitive to motion. The point analytic spectrum sequence has a high signal-to-noise ratio, insensitive to motion, with no strict requirements on uniform field and water suppression. However, the TE time is long (135-270ms), and it is difficult to find Short T2 metabolites. Therefore, the selection of hydrogen proton spectrum sequence is the key factor to obtain a meaningful metabolite data of glioma. Currently, the research and application of craniocerebral MRS mainly adopts single voxel and multivoxel magnetic resonance imaging technology. Single voxel, i.e., the data acquisition is from a single voxel and its advantages are accurate localization, short acquisitioned time and high spectral resolution; the main drawback to this technology is its limitation, to the coverage of the anatomical site, i.e., only an area can be analyzed at a time. The region of interest of multivoxel technology is larger and the voxel is smaller, which can obtain the spectra of multiple heterogeneous lesion and normal tissues in a larger field of view. However, the localization of superficial lesions in the brain is easily interrupted by the skull and adjacent structures.

3. Factors influencing brain ¹H-MRS imaging:

The main factors affecting MRS sensitivity are metabolite concentration, magnetic field strength, uniformity, equipped water pressure, voxel size and position, signal-to-noise ratio, spatial resolution, etc. In practice, before the start of a scan, in order to obtain high quality spectral image, the scanning should be strictly homogenized, water and fat suppressed. And, the location should avoid blood vessels, blood components, air, cerebrospinal fluid, fat, necrotic areas, metals, calcification and bones, so as to reduce the impact on its image.

The value of MRS in the diagnosis of glioma:

1. Differential diagnosis of brain tumor:

At present, NAA is only found in the brain, which are produced by mitochondria of neuron cells, represents neuronal activity and density; Cr exists in neurons and glial cells, which acts as a buffer between ATP and ADP, by storing high-energy phosphate bonds in brain cells. There are no neurons outside the brain, so the peak of NAA wave and Cr, cannot be detected in the hydrogen proton spectrum. For example, meningioma and schwannoma metastasis belongs to the lesion of extracerebral tumor; so as, MRS can be used as an effective method for the differential diagnosis of intracerebral and extracerebral tumors [6]. If there are

peaks of NAA and Cr in extracerebral tumors, there might be two reasons [7, 8]: either the extracerebral tumor infiltrates the brain tissue or the region of interest of the spectral examination exceeds the range of the tumor, including part of the brain tissue.

2. Differentiation between neoplastic and non-neoplastic disease:

Hydrogen proton spectrum can distinguish brain tumors and non-tumor lesions with similar performance on conventional MR, and its accuracy rate can be as high as 95%~100% [9, 10]. Combined with routine MR performance, the accuracy of the diagnosis, can be high yield. CHO wave change is a marker of brain tumor specificity; an increase in CHO wave and CHO/Cr ratio, strongly suggests brain tumor [11, 12]. Most studies showed that almost all tumors with CHO/Cr ratios, were greater than 2. When CHO/Cr ratio was greater than 2, the sensitivity and the specificity of diagnosing brain tumors were 96% and 70%, respectively. When the CHO/Cr ratio was greater than 2.5, the sensitivity of diagnosing brain tumor reduced to 90%, but the specificity increased to 86%. The CHO/Cr ratio of some non-neoplastic lesions could also be greater than 2, but CHO wave were generally not higher than that of the contralateral normal brain tissue. In the following cases, the hydrogen proton spectra of the brain tumors, may be misidentified, as non-neoplastic lesions. (1) CHO wave can be absent when there is obvious necrosis in the tumor, and sometimes it cannot be identified with cystic non-neoplastic lesion. CHO wave can be easily identified by using long TE. However, on short TE scans, Ace and Ala peak can appear, in infectious lesion. Cysticercosis is caused by the infection of parasites; Ace and Ala can be detected, but AA peak is not found; while characteristic AA peak, can be seen in the necrotic area of the brain abscess. (2) The hydrogen proton spectrum of a benign glioma can be similar to the normal brain parenchyma. Following demyelination, CHO wave in the tumor, can be lower than that of the normal brain tissue, in the contralateral side; but, the CHO/NAA ratio is higher, to the contralateral side [13]. (3) When the tumor is precisely small, a large number of normal brain tissues are included in the region of interest of the spectral examination, which may provocate misdiagnosis. (4) In inflammatory pseudo-tumor, demyelinating lesion and viral encephalitis, the hydrogen proton spectrum performance can be similar, as in an invasive brain tumor; the increase of CHO wave is mainly caused by gliosis, but the ratio of NAA/Cr is basically normal on the hydrogen proton spectrum, which is different from that of the tumor [14].

3. Differential diagnosis of high and low grade gliomas:

The typical manifestation of glioma in MRS, is a significant decrease in NAA wave, following an abnormal division and proliferation of glial cells, that invade normal neurons and cause their loss or decline in function. A rise in CHO peak could be noteworthy in all grades of glioma due to vigorous proliferation of tumor cells, besides an increase in membrane turnover; but, the rise is more significant in high-grade glioma; the higher the grade of the tumor, the more energy it consumes during the process of proliferation, thus with a significant decrement in the Cr wave; Lac can appear, reflecting tumor hypoxia [15]. Studies suggests that glioma grading through hydrogen proton spectroscopy is more accurate than biopsy because it provides more areas of tissue metabolism than biopsy. The sensitivity, specificity and accuracy of hydrogen proton spectrum in the differentiation of benign and malignant gliomas were 100%, 86% and 96%, respectively [13, 16]. CHO/NAA ratio, CHO/Cr ratio and NAA/Cr ratio, are commonly used to evaluate, benign and malignant glioma. There were significant differences in CHO/NAA ratio,

CHO/Cr ratio and NAA/Cr ratio; among which, CHO/NAA ratio and CHO/Cr ratio, are more significant in the determination of benign and malignant glioma [10, 12, 17, 18]. The higher the grade of the tumor, the higher is the CHO/NAA ratio and CHO/Cr ratio; the presence and elevation of Lip and Lac waves are common in malignant glioma with necrosis. However, MI wave can also be seen, closely related to the grade of the tumor; the MI/Cr ratio of benign glioma was significantly higher than that of the malignant glioma [19].

4. Histological indications in tumor:

Hydrogen proton spectroscopy may indicate the type of tumor tissue; despite, difficulties distinguishing primary lymphoma of the central nervous system from glioma, there are obvious Lip waves in the solid part of the tumor, which are specific for the diagnosis of lymphoma [20]; studies at home and abroad, have found that Lip is closely related to the apoptosis of lymphoma; thus, the higher is the apoptosis of lymphoid cells, the higher is the lipid peak [21, 22]. However, an ascent of Lip wave, in the tumor of the sellar region, indicates craniopharyngioma [23]. The malignant degree of primitive neuroectodermal tumor is higher than that of glioma; thus, the ratio of CHO/Cr and CHO/NAA is significantly higher than that of astrocytoma and ependymoma. The presence of glycine peak within the tumor parenchyma of the lateral ventricle might suggest, the tumor of the central nervous system, in origin [24]. MRS features of a glycine peak at 3.5ppm can be detected in both, in vivo and in vitro. Glycine is an important neurotransmitter in immature neurons, so it appears in the tumors of the central nervous system, characterized by immature cells.

5. Application in tumor puncture:

At present, stereotactic biopsy is often used to grade multiple lesions, deep or functional areas. If the biopsy specimen, is deprived of the part with the highest degree of tumor malignancy, the pathological grade obtained, might be inaccurate [25]. The most obvious part of tumor enhancement is often selected as the target of traditional biopsy, which can improve the biopsy accuracy, to some extent. However, many scholars at home and abroad, have found that, about 30% of high-grade gliomas show non-enhanced characteristics; therefore, a non-invasive imaging method is urgently needed to separate the boundaries of tumor tissues, from normal brain tissues, and to display the heterogeneity in tumor tissues [26, 27]. Hydrogen proton magnetic resonance spectroscopy, can automatically merge, frameless stereotactic biopsy technology, to achieve the selection of biopsy targets, from the metabolic level. However, controversies exist, on which metabolic index, should be implemented, to select the target of glioma. Stadbauer et al. [28] successfully integrated MRS and MR through third party software, applied the frame free stereoscopic orientation system, performed accurate biopsy with CHO/NAA metabolic ratio, and used this technology to accurately determine the tumor boundary. Moreover, the abnormal boundary of tumor metabolism, shown by the Gaussian distribution of CHO/NAA, was compared with the abnormal signal boundary of T2, which was verified by biopsy. It was found that MRS could more accurately display the extent of the tumor than the conventional sequence. At present, most studies at home and abroad, have found that, CHO/NAA index has good sensitivity, specificity and accuracy; among which, CHO is linearly correlated with Ki67 index; while CHO/NAA and CHO/Cr, are positively correlated with tumor cell density, in stereotactic biopsy target specimens [29, 30]. The study also found that CHO/NAA was an indicator with the strongest correlation, to the tumor level; suggesting, the higher the ratio of

CHO/NAA in glioma, the higher was the malignant degree of the tumor. Therefore, CHO/NAA was the preferred metabolic indicator of the target, in the current spectroscopy-guided puncture biopsy [31, 32]. Through the frameless stereotactic biopsy technology, based on automatic fusion of ^{1}H-MRS images, we can determine the location of biopsy target specimens from the metabolic level, which is helpful to improve the positive rate of biopsy; as well, provides the basis for making an appropriate treatment plan, before the operation. It is believed that this method will be widely used in clinical practice in the future and will continue to develop and improve.

6. Differentiation between tumor recurrence and radiation necrosis:

Radiotherapy is an important adjunctive therapy following the operation for glioma, and radio necrosis is a common and serious complication of radiotherapy. Postoperative recurrence of glioma and radiation necrosis, have extremely similar clinical manifestation and conventional MRI morphological changes; and, the identification of the both, is of great clinical significance for the selection of treatment methods; while routine examination is of limited value in the differential diagnosis, in both of the conditions. ^{1}H-MRS can sensitively detect the changes of metabolites in the tissues of an abnormally enhanced MR sequence, such as CHO/CR, CHO/NAA, NAA/Cr, etc. [33]. The recurrence of glioma leads to the proliferation of tumor cell membrane and cellular proliferation of the adjacent lesion; and, the release of glial reactive hyperplasia and inflammatory cells, can lead to a significant increase in CHO peak. At the same time, as to the destruction of normal neurons by tumor, the number of normal neurons are reduced and the nerve fibers are ruptured, resulting in a significant reduction of NAA; radio-necrosis can also cause neuronal injury, demyelination, blood-brain barrier destruction, edema, and inflammatory cell infiltration, which results in reduction of NAA [34, 35]. Prospective studies, at home and abroad, have found that [36], MRS following recurrence of glioma showed decrement or disappearance of NAA peak, significantly increased CHO peak, increased CHO/NAA ratio, increased CHO/Cr ratio, decreased NAA/Cr ratio, decreased CHO peak of necrotic tissue, decreased NAA peak, and with a basically normal Cr peak. However, the value of NAA/Cr, Lac and Lip, in the differential diagnosis of the both, remained controversial.

7. Assessment for the range of tumor:

Surgical resection is the mainstay of treatment for glioma. However, the characteristics of an invasive growth of glioma, makes it difficult to remove the tumor tissue, completely [37]. It is generally believed that the boundaries of the tumor, on conventional MRI, are the tumor enhanced margins and the peritumoral areas of abnormal signal intensity on T2WI, which are used to determine the scope of surgery and radiotherapy. However, a growing number of studies have found that, the peritumoral edema in glioma, is not only an angiogenic edema, but also contributes to a large number of tumor cells along the new blood vessels, which have an invasive growth pattern. Its range is often beyond the range of enhancement, during an MR enhanced scanning; and, the evaluation of tumor range, by enhancement, is obviously inaccurate; so, the range of tumor invasion, should be reflected by hydrogen proton wave harmonic cerebral perfusion [38]. Therefore, it is clinically significant, to determine the invasive range of glioma, for determining and implementing, the range and scope of surgery and radiotherapy. Currently, most scholars have found that [38, 39], the value of hydrogen proton spectroscopic parameters, CHO/Cr, NAA/CHO and NAA/Cr, have clear statistical significance, in the

evaluation of the range of tumor cell infiltration and tumor invasiveness, in the peritumoral region of glioma; among which, CHO/Cr is highly characterized; while, the value of Lac for confirmation of the boundary, is still controversial.

Expectation:

^{1}H-MRS has a unique advantage in the diagnosis, differential diagnosis, classification, defining the scope of the tumor, preoperative guidance and postoperative evaluation of glioma. There are limitations to its clinical application due to various factors affecting it. However, as an important adjuvant, to conventional MRI, MRS has its unique application value. With ongoing advancement and research, application of MRS has a broader prospective, in glioma and other brain tumors.

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