Review Article

The Use of Proton MR Spectroscopy in Epilepsy: A Methodological Review

Neda Mohammadi Mobarakeh [1,2], Fatemeh Fadaie [3], Mohammad Reza Nazem Zadeh [2], Jafar Mehvari Habibabadi [4], Hamidreza Saligheh Rad [1,2,*]

[1] Quantitative Medical Imaging and Spectroscopy Group, Research Center for Molecular and Cellular Imaging, Tehran, Iran

[2] Department of Biomedical Engineering and Medical Physics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[3] Department of Epilepsy, Pars Hospital, Tehran, Iran

[4] Department of Neurology, Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Received: 04 December 2018

Accepted: 05 February 2019

http://FBT.tums.ac.ir

Keywords:

Proton Magnetic Resonance Spectroscopy;

Epilepsy;

Temporal Lobe Epilepsy;

Juvenile Myoclonic Epilepsy;

Generalized Epilepsy.

Abstract

Magnetic Resonance Spectroscopy (MRS) has at least two major roles in the evaluation of epileptic patients. First, MRS can help to understand the interaction between seizures and metabolic function. Thus, MRS is particularly interesting for basic science studies of seizures and epilepsy. Second, MRS can explain the nature of seizure control and/or provide localization information by measuring metabolic changes. So MRS can be used as a powerful complementary technique to structural MRI for diagnosis and assessment of response to therapy, and measurement of disease progression. The aim of this paper is to review the methodological aspects of ^{1}H-MRS publications between 1994 to 2016, which utilized ^{1}H-MRS in lateralizing the epileptogenic zone in lesional and non-lesional Temporal Lobe Epilepsy (TLE), Extra-Temporal Lobe Epilepsy (ETLE), and generalized epileptic patients to help the spectroscopist, magnetic resonance imaging technologists, and radiologists to improve the overall diagnostic sensitivity in epileptic patients.

1. Introduction

According to the World Health Organization (WHO), more than 50 million individuals are living with epilepsy, of whom nearly 80% are in middle- and low-income countries and do not get the proper treatment. Approximately 2.4 million individuals are diagnosed with epilepsy annually, and about 0.2% of all deaths in the world occur among this group of patients every year [1].

The first suggested treatment line for patients with epilepsy is Antiepileptic Drugs (AEDs). Although most patients with generalized seizures and a considerable number of patients with partial epilepsy respond well to antiepileptic drugs, 20-30% of patients in the focal epilepsy category are resistant to the current medications [2]. Surgical resection of seizure foci is frequently one of the most effective treatments for this group of patients. Defining the exact resection margin is crucial in the surgical treatment of epilepsy to remove the epileptogenic zone as much as possible.

Pre-surgical planning for epilepsy surgery includes an extensive medical history, physical exam,

Corresponding Author:

Hamidreza Saligheh Rad, PhD

Quantitative Medical Imaging and Spectroscopy Group, Research Center for Molecular and Cellular Imaging, Tehran, Iran

Tel: (+98) 2188973653 – 108, Fax: (+98) 2166466383.

E-mail: h-salighehrad@tums.ac.ir

Electroencephalogram (EEG) findings, and neuroimaging information. Structural and functional neuroimaging methods, including Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) have a key role in evaluating and selecting patients for surgery. However, advancements in imaging techniques such as Diffusion Tensor Imaging (DTI), MRI morphometry, Magnetic Resonance Spectroscopy (MRS), EEG–fMRI (functional MRI), Magnetoencephalography (MEG)/Magnetic Source Imaging (MSI), and EEG/ESI (Electronic Source Imaging) can improve surgical decision making noticeably [3].

Cellular and biochemical changes occur before structural damage can be detectable by conventional imaging. In addition, there are cases where conventional MRI cannot demonstrate structural changes. Methods such as MRS that discover biochemical changes in the tissue are perfectly suited to assessing such pathological changes even in the absence of morphological alterations. Therefore, MRS can be used as a powerful complementary technique to structural MRI for diagnosis, response to therapy and measurement of disease progression.

Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) identifies hydrogen atoms and uses the same principles of physics as MRI to obtain the biochemical information of tissue metabolites by detecting their resonance frequencies, referred to as chemical shift. MRS can measure concentrations of different metabolites in various structures and different pathological situations of the brain to generate sensible and reliable results.

MRS has at least two major roles in the evaluation of epileptic patients. First, MRS can help to understand the interaction between seizures and metabolic function through the study of the relationship between the clinical characteristics of seizures and ^{1}H-MRS alternations. Therefore, MRS is particularly interesting for basic science studies of seizures and epilepsy [4, 5]. Second, MRS can explain the nature of seizure control and/or provide localization information by measuring metabolic changes [6, 7]. On the other hand, no study has reviewed the literature based on methodology and its contribution to^{1}H-MRS results in epilepsy although there is significant methodological variability among the relevant studies. Therefore, this paper is designed in such a way that it can provide an overview of the findings of 99 ^{1}H-MRS studies on patients with epilepsy based on various methodological and technical aspects, including the strength of the magnetic field, MRS sequence, and absolute concentration versus metabolite ratios.

2. Methodological Considerations for ^{1}H-MRS Studies

2.1. Literature Review

We obtained 250 papers through the electronic databases of Medline/PubMed and ScienceDirect from 1994 to 2016 (Table 1, 2, 3). The search terms were epilepsy, Temporal Lobe Epilepsy (TLE), generalized epilepsy, Juvenile Myoclonic Epilepsy (JME), hippocampus, Frontal Lobe Epilepsy (FLE), Hippocampal Sclerosis (HS), and correlation, which were also combined with proton magnetic resonance spectroscopy, proton MR spectroscopy, ^{1}H MRS, neuroimaging, and EEG. We excluded studies which included children or had already been published in pediatric journals and included studies on patients with HS lesions on MR imaging. Two reviewers studied the titles and abstracts of the studies and excluded some papers because of a lack of necessary criteria for patients or methodology and studied 107 papers based on methodological aspects. A summary of the details of all included studies was tabulated into a spreadsheet. Then, these studies were classified into three groups (generalized epilepsy, TLE, ETLE researches) and seven methodological factors were extracted from them.

2.2. MRS in Epilepsy

The most popular metabolites studied in epileptic patients include N-Acetyl Aspartate (NAA, 2.01 p.p.m.), Creatine (Cr, 3.0 p.p.m.), and Choline (Cho, 3.2 p.p.m.). NAA is considered as a neuronal and axonal integrity marker; Cr and Cho are found in neurons and glia. On the other hand, Cr is a key component of Phosphocreatine (PCr) and it can be considered a normalization factor for the bioenergetics parameter [8].

Several groups have suggested that MRS can be used as a biomarker to assess the mechanism of treatment failure and may have a role in the pre-surgical evaluation of refractory Temporal Lobe Epilepsy (TLE), especially when conventional MRI cannot reveal any abnormality [9-11]. Cendes *et al.* performed Magnetic Resonance Spectroscopy Imaging (MRSI) and volumetric analysis in 100 refractory TLE patients. They found that the combination of these two methods can lateralize TLE accurately in the great majority of patients (90% by combining the two methods, 86% using MRSI, 83% using MR volumetry, and 93% by EEG) [10]. Moreover, ^{1}H-MRS studies on MRI-negative patients have provided evidence of reduced NAA/Cr and/or NAA/Cho ratios in the seizure focus, e.g. thalamic and frontal lobe in Idiopathic Generalized Epilepsy (IGE) and Frontal Lobe Epilepsy (FLE) patients, respectively [5, 12, 13].

On the other hand, ^{1}H-MRS is a non-invasive and sensitive method to help detecting subtle variations for Extra-Temporal Lobe Epilepsy (ETLE) patients even in the absence of structural alterations [10, 11]. Moreover, it has been shown that ^{1}H-MRS has successfully identified processes of epileptogenesis in Juvenile Myoclonic Epilepsy (JME), which was characterized by a reduction of NAA levels in the thalami and prefrontal cortex of this group of patients [14]. ^{1}H-MRS was able to reveal elevated levels of Glutamate (Glu) and Glutamine (Gln) (Glu+ Gln= Glx) and Gamma-Aminobutyric Acid (GABA) in the frontal and occipital lobes of IGE patients [15, 16].

2.3. General Considerations

There are only a few factors which affect the information content of the proton spectra of the brain, including the type of the pulse sequence, TE, and field strength. Despite the use of ^{1}H-MRS as a non-invasive method for investigating brain neurochemistry for understanding psychiatric and neurological diseases, a low Signal-to-Noise Ratio (SNR) has limited its use in clinical investigations. On the other hand, due to an approximately linear increase in the noise voltage with frequency, it is expected that SNR increases linearly with B_0. In recent years, thanks to the increased field strength of scanners and improved acquisition techniques and analysis approaches, ^{1}H-MRS has gained the support and interest of the MR and clinical neuroscience communities [8].

At 1.5 T field strength with long TE, signals from Cr, Cho, and NAA are easily detectable in a normal brain where other chemical compounds such as Alanine and Lactate (Lac) may be observable due to some pathological processes. At short TE, chemical compounds such as Glutamate (Glu), Glutamine (Gln), GABA, Myo-Inositol (mI), lipids and macromolecules can be observed. After increasing the field strength to 3, 4, and 7 T, spectral resolution increases and more components can be recognized with high confidence [8].

Currently, multi-voxel MRS (Chemical Shift Imaging (CSI) or MRSI) and Single-Voxel Spectroscopy (SVS) are two methods of obtaining the spatially localized biochemical information in epilepsy. SVS is a simple and rapid image acquisition technique (2-4 min), but has some limitations such as the voxel position. The SVS voxel should contain the lesion correctly during patient examination. In other words, it should be carefully positioned on the tissue. MRSI can help overcome this limitation by changing the grid to fit precisely over the desired lesion any time during data acquisition. MRSI is important in obtaining spatial information on small structures like amygdala or hippocampus, and SVS is preferred when comparing a pathological zone with a contralateral region. Therefore, whether to choose SVS or MRSI depends heavily on the aim of the study (See [8] for more details).

Both types of localization techniques can use various types of pulse sequences. Point Resolved Surface coil Spectroscopy (PRESS) and Stimulated Emission Acquisition Mode (STEAM) are the two most common pulse sequences that the single-voxel technique uses. PRESS excitation is the most common method for two or three-dimensional MRSI. For more information about PRESS, see [17], and for a detailed comparison between STEAM and PRESS, see [18].

Two parameters, TE and TR are effective on the ^{1}H-MRS results and should be determined based on the desired metabolite. MR spectra at short TE (based on our knowledge from ^{1}H-MRS studies in epilepsy "20-72 ms") involve broad macromolecule resonances signals that decay completely after 60-80 ms because of their

short T2 relaxation time. However, spectra obtained at short TE values are richer in information because MR spectra obtained using short TE provide more metabolite signals, including Glx or mI (increased Glx levels may reflect seizure activity). The quantification of long TE (107-272 ms) acquisitions is less sensitive to measurement and tissue conditions compared to signals measured at short TE values. SNR and then quantification shall be improved by using a long TR (>3 seconds, about 3000-6000 ms), whereas examination time increases. The typical in-vivo TR value for clinical MRS is in the range of 1-3 sec. Nevertheless, it is necessary to use long TR by keeping TE as short as possible, so that T1 and T2 relaxation do not affect signal intensities. Therefore, choosing between short and long TE along with appropriate TR depends on the aim of the study; for example, if only NAA, Cho, and Cr need to be quantified, ^{1}H-MRS must be performed at long TE to prevent the effects of macromolecular signals on the quantification procedure [8].

2.4. Methodological Review of Hippocampal ^{1}H-MRS Studies in TLE

There are methodological differences in the hippocampal ^{1}H-MRS in TLE studies published to date. Our investigation of 78 papers showed that they had all been carried out with different MR scanners (e.g. Philips, General Electric, Siemens) running at a field strength of 1.5 Tesla (T), except for 18 of them: four studies used 2 T equipment [4, 19-21], seven studies used 3 T [22-28], three studies used 4 T [29-31], four studies used 4.1 T [9, 32-34], and one study used 7 T [35]. Most of these studies used the acquisition technique of SVS with the PRESS sequence and long TE in the range of 107-288 ms and TR between 1500 and 5000 ms, whereas four studies preferred the STEAM sequence [21, 23, 24, 36] and one study used 3D Echo Planar whole brain Spectroscopic Imaging (EPSI) [30].

One of the most important issues in hippocampal ^{1}H-MRS studies in TLE patients is the size of investigated voxels, ranging from 1 cm^3 to 6 cm^3. Because of the hippocampal structure in which the middle part and the tail end are considerably thinner than the edge lengths, the voxel size often contains extra tissue beyond the hippocampus, which can lead to partial volume effects. Chang *et al.* obtained spectra from hippocampal areas bilaterally with VOIs of 2.25 cm^3 and 6 cm^3 in healthy and patients groups. They found that the overall lateralization ability of MRS was 72% and the correct lateralization rate was 82% for the VOI of 2.25 cm^3 (1.5×1.5×1 cm^3) and 62% for the VOI of 6 cm^3 [37]. Moreover, tissue heterogeneity in the selected VOIs is also another important factor which has been addressed in several studies. The differences in the concentration of metabolites between Gray Matter (GM) and White Matter (WM) [38], in medial and lateral temporal lobe [39], and at different positions along the hippocampus [39-41] are those relevant examples. Table 1 shows a comparison of methodological aspects for hippocampus in TLE patients. Based on our current knowledge, the two most popular voxel sizes are 2×2×2 cm^3 and 1.5×1.5×1.5 cm^3, and the most popular sequence is PRESS with long TE but as discussed above, the choice between short and long TE along with appropriate TR depends on the aim of the study.

On the other hand, the literature has usually suggested ^{1}H-MRS as a supplementary tool in the interictal localization of seizure foci. In six studies the possible role of this modality was studied in the ictal and postictal phases [42-47]. F. Fadaie *et al.* showed significant decreases in the NAA/Cr, NAA/Cho, and NAA/Cr+Cho ratios immediately after ictus in the ipsilateral hippocampus compared with the contralateral hippocampus of patients and controls. They showed that the metabolite ratios in the interictal phase of the three groups were not significantly different [42]. Maton *et al.* showed that in patients with TLE, there were no significant differences in metabolite ratios in the ictal versus the interictal phase [44]. The post-ictal period of MRS acquisition might be one factor that affects the results in such studies. Simister *et al.* showed that change in Cr144/Cr30 and NAAt144/Cr144 ratios correlated with the post-ictal interval [46].

Mohammadi *et al.* suggested an interesting approach for the quantification of MRS data. They employed a dimension reduction technique for the spectral fitting of the MR spectroscopy data with short TE (=30 ms) and showed that the sensitivity and specificity of this modality in TLE patients are 60% and 82%, respectively [48].

Table 1. Comparison of methodological aspects (^{1}H-MRS protocols, analysis software) for hippocampus in TLE patients

#	Study Author (year)	Strength of Magnetic Field/Vendor (Tesla)	TE/TR (ms)	^{1}H-MRS Sequence	Localization Techniques	Metabolic Result	Quantification Software
1	F. Riederer *et al.* (2006)	3 Bruker Medspec	20/2500	STEAM	SVS	NAA, Glx, Glu, Gln, mI, mI/Cr, Cho, tCr	LCModel
2	F. Riederer *et al.* (2007)	3 Bruker Medspec	20/2500	STEAM	SVS	NAA	LCModel
3	M. Brazdil *et al.* (2009)	1.5 Siemens	80/1500	PRESS	SVS/CSI	NAA, NAA/Cr, NAA/Cr+Cho	LCModel
4	D. Fojtiková *et al.* (2007)	1.5 Siemens	80/1500	-/PRESS	SVS/CSI	NAA, NAA/Cr, NAA/Cr+Cho	LCModel
5	M. Hajek *et al.* (2009)	1.5 Siemens	135/5000	PRESS	SVS	NAA/Cr,NAA/Cho,NAA/Cr+Cho, Cho/Cr	LCModel
6	L. Hanoglu *et al.* (2004)	1.5 GE	144/1500	PRESS	SVS	NAA/Cho+Cr	-
7	H. Aydin *et al.* (2012)	1.5 Philips	26, 144/1500	PRESS	CSI	Lac, phosphocreatine, NAA, Cr, Cho, mI, Glx, NAA/Cr, NAA/Cho+Cr, Cho/Cr	Philips software
8	E. Achten *et al.* (1998)	1.5	135/1600	-	SVS	NAA/Cho+Cr	-
9	E. Achten *et al.* (1997)	1.5	135/1600	-	SVS	NAA/Cho+Cr, NAA/Cr, NAA/Cho, Cho/Cr, NAA	-
10	G. Lantz *et al.* (2006)	1.5 Eclipse, Philips	288/1600	PRESS	SVS	NAA/Cho+Cr, NAA/Cr,	SAGE spectroscopy

						NAA/Cho, Cho, Cr, NAA	analysis software
11	F. Zubler *et al.* (2003)	1.5 Marconi Medical	270/1600	PRESS	SVS	NAA/Cho+Cr	SAGE spectroscopy analysis software
12	C. O. Duc *et al.* (1998)	1.5 Philips	136/6000	PRESS	SVS	NAA, Cr, Cho	DEC workstations using a home-built processing software based on DI 3000
13	G. R. Ende *et al.* (1997)	1.5 GE	135/1800	PRESS	CSI	NAA/Cho+Cr, NAA/Cr, NAA/Cho, Cho, Cr, NAA	software provided by Siemens (LUISE)
14	P. Vermath en *et al.* (2002)	1.5 Siemens	135/1800	PRESS 2D	CSI	NAA, Cr, Cho	-
15	P.A. Garcia *et al.* (1997)	2 Philips	-	3D	CSI	NAA/Cr	NMR1(NewMe thods esearch, Syracuse,NY, USA)
16	S. G. Mueller *et al.* (2011)	4 Siemens	45/1750	3D echo planar whole brain spectroscopi c imaging (EPSI)		NAA/Cho+Cr	SPM2
17	J. W. Hugg *et al.* (1993)	2 Philips	272/1700	3D PRESS	CSI	NAA, Cho, Lac	-
18	A. A. Capizzan o *et al.* (2002)	1.5 Siemens	135/1800	PRESS 2D,3D	CSI	NAA, NAA/Cr+Cho	-
19	A. A. Capizzan o *et al.* (2001)	1.5 Siemens	135/1800	PRESS	CSI	NAA	software developed in our laboratory
20	P. Vermath en *et al.* (2000)	1.5 Siemens	-		CSI	NAA/Cho+Cr, NAA, Cr, Cho	LUISE; Siemens
21	P. Vermath en *et al.* (2003)	1.5 Siemens	140/1800	-	CSI	NAA/Cho+Cr	Luise Siemens

22	J. W.Pan *et al.* (2013)	7 Varian	40/1500	gradient-based slice-selective excitation (10-mm thick slices)	CSI	NAA/Cr	-
23	D. C. Spencer *et al.* (2005)	1.5 GE	144/1500	PRESS	CSI	NAA/Cr	AGE (SAGE Dev 2000.3, Minneapolis, MN, USA)
24	J.G. Burneo *et al.* (2004)	4.1	50/2000	-	CSI	NAA/Cr	NMR1(NewMethods esearch, Syracuse,NY, USA)
25	J. J. Shih *et al.* (2011)	1.5	135/1500	PRESS	SVS	NAA/Cho	Levenberg–Marquardt algorithm
26	J.J. Shih *et al.* (2004)	1.5 Picker edge	135/1500	PRESS	SVS	NAA/Cho	-
27	A. A. Cohen-Gadol *et al.* (2004)	4 Varian Inova	-	-	CSI	NAA/Cr	-
28	D. Lu *et al.* (1997)	1.5 GE	136/1600	PRESS	SVS	NAA/Cr+Cho	-
29	Sun-Won Park *et al.* (2001)	1.5	144,288/1500-2000	PRESS	SVS	NAA/Cr, NAA/Cho	-
30	Kee-Hyun Chang *et al.* (2000)	1.5 GE	136/1500	PRESS	SVS	NAA/Cr, NAA/Cho	-
31	S. K. Lee *et al.* (2005)	1.5 GE	136/1500	PRESS	SVS	NAA/Cr, NAA/Cho	In house using Levenberg–Marquardt algorithm
32	L. C. Meiners *et al.* (2000)	1.5	136/2000	PRESS	SVS	NAA/Cr, NAA/Cho	MRUI software
33	M.T. Doelken *et al.* (2008)	1.5 Siemens	30/3000	PRESS	SVS	tNAA, Cho, Cr, Glx, mI	LCModel

34	M.T. Doelken et al. (2007)	1.5 Siemens	30/3000	PRESS	SVS	tNAA, Glx, Cho, Cr, mI, NAA/Cho+Cr	LCModel
35	Th. Hammen et al. (2003)	1.5 Siemens	135/1500	-	CSI	NAA/Cho+Cr	MAGNETOM Vision system
36	E. Pauli et al. (2000)	1.5 Siemens	135/1500	2D CSI spin-echo protocol	CSI	NAA/Cho	Magnetom Vision system
37	E. Duzel et al. (2004)	1.5 GE	35/1500	PRESS	SVS	NAA/Cho+Cr	AMARES program
38	C. G. Choi et al. (1999)	2 Siemens	20/6000	STEAM	SVS	tNAA, tCr, Cho, mI	LCModel
39	Th. Hammen et al. (2007)	1.5 Siemens	30/3000	PRESS	SVS	tNAA, Cho, Cr, Glx, mI, NAA/Cho+Cr, NAA/Cr, tNAA/Cr	LCModel
40	Th. Hammen et al. (2008)	1.5 Siemens	30/3000	PRESS	SVS	tNAA mI, tNAA/Cr	LCModel
41	T. C. Ng et al. (1994)	1.5 Siemens	135/1500	double-echo pulse sequence	CSI	NAA/Cho	SA/GE software; GE Medical Systems, Milwaukee, Wis
42	Th. Hammen et al. (2006)	1.5 Siemens	30/3000	PRESS	SVS	Glx, mI, Cho, Cr, tNAA	LCModel
43	R. J. Simister et al. (2009)	1.5 GE	30/3000	PRESS	SVS	tNAA/Cr, Glx/Cr, GABA+/Cr	LCModel
44	F. G. Woermann et al. (1999)	1.5 GE	30/3000	PRESS	SVS	NAA, Cr, Cho, mI, Glx, NAA/Cr+Cho, NAA/mI, NAA/Glx	LCModel
45	A. Connelly et al. (1998)	1.5 Siemens	135/1600	PRESS	SVS	NAA, Cho, Cr, NAA/Cho+Cr	-
46	R. J. Simister et al. (2008)	1.5 GE	30,144/3000	PRESS	SVS	tNAA, Cr,Lac, Cho, mI, Glx, tNAA/Cr,	LCModel

						Glx/Cr, Cr144/Cr30	
47	R. J. Simister et al. (2002)	1.5 GE	30/3000	PRESS	CSI	tNAA, Glx, Cho, Cr, mI, tNAA/Cr, tNAA/Cho+Cr, tNAA/mI	LCModel
48	W. Serles et al. (1999)	1.5 Philips	272/2000	-	CSI	NAA/Cr	-
49	F. Cendes et al. (1997)	1.5 Philips	272/2000	PRESS	CSI	NAA/Cr	-
50	F. Cendes et al. (1995)	1.5 Philips	272/2000	-	CSI	NAA/Cr	-
51	F. Cendes et al. (1994)	1.5 Philips	272/2000	-	CSI	NAA/Cr	-
52	A. Bernasconi et al. (1999)	1.5 Philips	-	-	CSI	NAA/Cr	-
53	L. M. Li et al. (2000)	1.5 Philips	272/2000	-	CSI	NAA/Cr	locally developed software
54	L. M. Li et al. (2000)	1.5 Philips	272/2000	-	CSI	NAA/Cr	-
55	J. Zhang et al. (2014)	1.5 Siemens	107/4500	PRESS	SVS	NAA, Cho, Cr, NAA/Cr, NAA/Cho+Cr	software provided by Siemens on the Siemens MRI scanner
56	J Shen et al. (2009)	3 Philips	31/2000	2D PRESS	CSI	NAA/Cho+Cr, mI/Cr, Glx/Cr	the Intera Achieva 3.0 T MRI system
57	J. Qi et al. (2007)	2 Gyrex SGR	135/2000	PRESS	SVS	NAA/Cho+Cr, Cho/Cr,NAA/Cr	-
58	M. F. Chernov et al. (2009)	1.5 Toshiba	128,136/2000	-	SVS	NAA, Cho, Cr	software provided by the supplier (MRS-PRO/PX; Toshiba Medical Systems)

59	Y. Someya et al. (2000)	1.5 Philips	136/1500	-	-	NAA/Cho+Cr	-
60	S. Kikuchi et al. (2001)	1.5 GE	30/2000	PRESS	SVS	NAA/Cr	SA/GE, General Electric, WI, USA
61	T. Obata et al. (2004)	1.5 Philips	136/1500	-	SVS	NAA/Cho+Cr	-
62	M. Guye et al. (2002)	1.5 Siemens	136/1500/// 135/1600	2D in-house–designed acquisition-weighted//// PRESS	CSI/SVS	NAA/Cho+Cr	AMARES program
63	I. J. Namer et al. (1999)	3 Bruker	135/2000	PRESS	SVS	NAA/Cho+Cr	software package Paravision/UX NMR (Bruker)
64	M. A. S. Mantoan et al. (2009)	1.5 Siemens	135/1500	PRESS	SVS	NAA/Cho+Cr	(Leonardo, Syngo MR 2004 A
65	R. S. Briellmann et al. (2007)	3 GE	30/3000	PRESS	SVS	NAA, Cr, Cho, mI, Glx	LCModel
66	P. T. Meyer et al. (2001)	1.5 GE	35/2000	PRESS	SVS	NAA/Cr	-
67	H. Hetherington et al. (1995)	4.1	50/2000	-	CSI	Cr/NA, Cho/NA	NMR1 (Tripos, Syracuse, NY)
68	R. Kuznieckky et al. (1998)	4.1	50/2000\\\ 58/2000	2D PRESS	SVS/CSI	Cr/NA	-
69	S. M. Sawrie et al. (2001)	4.1	50/2000	PRESS	CSI	Cr/NA	-
70	B. Maton et al. (2001)	1.5 Philips	272/1500	-	CSI	NAA/Cho+Cr	NMR1 (Tripos, Syracuse, NY)
71	J. W. Pan et al. (2012)	4 Varian Inova	72\2000	-	CSI	NAA/Cr	-

72	K. N. Fountas et al. (2012)	3 GE	35/1500	PRESS	SVS	NAA/Cr, NAA/Cho, NAA/Cho+Cr	-
73	M. Castillo et al. (2001)	1.5	270,135/1500	PRESS	SVS	NAA/Cr	-
74	J. A. Mendes-Ribeiro et al. (1998)	1.5 Siemens	270/3000	STEAM	SVS	NAA/Cr, NAA/Cho, Cho/Cr	lack the appropriate software
75	F. Fadaie et al. (2016)	1.5 Siemens	135/1200	PRESS	CSI	NAA/Cr+Cho, NAA/Cho, NAA/Cr	Subtract_QUEST algorithm
76	J. Zhang et al. (2014)	1.5 Siemens	107/4500	PRESS	SVS	NAA, Cr, Cho, NAA/(Cho + Cr), NAA/Cr	software provided by Siemens on the Siemens MRI scanner
77	M. Y. Xu et al. (2015)	3 GE	35/1500	PRESS	SVS	NAA, Cr, Cho, NAA/(Cho + Cr), NAA/Cr	-
78	R. MarkWellard et al. (2003)	1.5 GE	35/1500	PRESS	SVS	NA, Cho, Cr, Glx, mI	LCModel

Table 2. Comparison of methodological aspects (^{1}H-MRS protocols, analysis software) in ETLE patients

#	Study Author (year)	Strength of Magnetic Field/Vendor (Tesla)	TE/TR (ms)	^{1}H-MRS Sequence	Localization Techniques	Metabolic Result	Quantification Software
1	P. Krsek at al. (2007)	1.5 Siemens	135/1500	PRESS	CSI	NAA/Cho, NAA/Cr, Cho/Cr	LC-Model
2	M. Guye at al. (2005)	1.5 Siemens	136/1500	2D, 1D in-house-designed acquisition-weighted	CSI	NAA/Cr, NAA/Cho+Cr	AMARES
3	J. W.Pan at al. (2013)	7 Varian	40/1500	gradient-based slice-	CSI	NAA/Cr	-

				selective excitation			
4	P.A. Garcia at al. (1997)	2 Philips	-	3D	CSI	NAA/Cr	NMR1(NewMethods esearch, Syracuse,NY, USA)
5	P. A. Garcia at al. (1995)	2 Philips	-	-	CSI	NAA/Cr, Cho/Cr	NMR1(NewMethods esearch, Syracuse,NY, USA)
6	S. G. Mueller at al. (2004)	1.5 Siemens	135/1800	-	CSI	NAA/Cr, NAA/Cho	A fully automated spectral-fitting software package developed in this laboratory
7	R. J. Simister at al. (2003)	1.5 GE	30/3000, 68/2000	PRESS, DQF sequence was applied to the same PRESS-localised volume	SVS	tNAA, Glx, Cho, Cr, mI, GABA+, tNAA/Cr, Glx/mI	LCModel
8	R. J. Simister at al. (2008)	1.5 GE	144,30/3000	PRESS	SVS	tNAA, Cr,Lac, Cho, mI, Glx, tNAA/Cr, Glx/Cr, Cr144/Cr30	LC-Model
9	J. W. Pan at al. (2012)	4 Varian Inova	72\2000	-	CSI	NAA/Cr	-
10	W. Serles at al. (1999)	1.5 Philips	272/2000	-	CSI	NAA/Cr	-
11	L. M. Li at al. (2000)	1.5 Philips	272/2000	-	CSI	NAA/Cr	-
12	J. A. Stanley at al. (1998)	1.5 Philips	272/	2D	CSI	NAA/Cho, NAA/Cr, Cho/Cr, Lac/Cr, NAA/Cr+Cho	Fitmasters program, Philips Medical Systems, Best, The Netherlands
13	R. A. A. Leite at al. (2013)	1.5 GE	135/1500	PRESS	CSI	NAA/Cho, NAA/Cr, NAA/Cho+Cr, Cho/Cr	work station Sun 60– Ultrasparc

14	D. Fojtiková et al. (2007)	1.5 Siemens	80/1500	-/PRESS	SVS/CSI	NAA, NAA/Cr, NAA/Cr+Cho	LCModel

Table 3. Comparison of methodological aspects (^{1}H-MRS protocols, analysis software) in generalized epileptic patients

#	Study Author (year)	strength of magnetic field/vendor (Tesla)	TE/TR (ms)	^{1}H-MRS sequence	localization techniques	Metabolic result	Quantification software
1	A. J. Ristić et al. (2011)	1.5 Siemens	135/1500	3D PRESS	CSI	Cho/tCr, NAA/tCr, NAA/Cho, NAA/Cho+tCr	Syngo Multi-Modality Workplace version VE23A
2	A. Bernasconi et al. (2003)	1.5 Philips	272/2000	-	CSI	NAA/Cr	in-house software
3	D. Fojtikova et al. (2006)	1.5 Siemens	80/1360	-	CSI	NAA/Cr	software supplied by the scanner producer
4	S. B. Mory et al. (2003)	2 Elscint Prestige	135/1500	PRESS	SVS	NAA/Cr	software supplied by the machine manufacturer
5	K. Lin et al. (2009)	1.5 Siemens	30/1500	2D PRESS	CSI	NAA/Cr, Glx/Cr	Syngo MR Spectroscopy Evaluation Programme– Syngo v.2004A
6	I. Savic et al. (2000)	1.5 GE	30/6000	STEAM	SVS	NAA, Cho, Cr, mI	LCModel
7	I. Savic et al. (2004)	1.5 GE	30/6000	STEAM	SVS	NAA, Cho, Cr, mI	LCModel
8	M.T. Doelken et al. (2010)	3 Siemens	30/1700	2D PRESS	CSI	tNAA, Glx, Cho, Glu, mI	LCModel
9	C. Haki et al. (2007)	1.5 Siemens	135,270/1500	PRESS	SVS	NAA, NAA/Cr	software provided by Siemens
10	S. C. Kabay et al. (2010)	1.5 GE	144/1000	2D PRESS	CSI	NAA, NAA/Cr	Advanced function software by GE Healthcare

11	R. J. Simister et al. (2003)	1.5 GE	30/3000	PRESS, the DQF sequence	SVS	tNAA, Glx, Cho, Glu, mI, tNAA/Cr, Glx/tNAA, Glx/mI	LCModel
12	D. Flügel et al. (2006)	1.5 GE	30/3000	PRESS	SVS	Cho, Cr, mI, NAA, Glx, Macromolecules	LCModel
13	R. MarkWellard et al. (2003)	1.5 GE	35/1500	PRESS	SVS	NA, Cho, Cr, Glx, mI	LCModel

2.5. Methodological Review of Extra-hippocampal ^{1}H-MRS Studies in TLE

We studied 16 papers in this area. In some studies, authors have examined a set of brain structures and regions that are anatomically and functionally associated with the epileptogenic zone (hippocampus) in TLE patients. This network includes the thalamus, temporal pole, basal ganglia, and insula. There are no significant differences in the reported methodology of ^{1}H-MRS studies regarding extra-hippocampal metabolite abnormalities in patients with TLE. All studies have used a 1.5 T scanner except for three [26, 29, 30]. One study has employed the EPSI sequence [30] whereas the others have used the PRESS sequence to obtain spectra from regions. The values of TE and TR used here are TE = 30-270 ms, and TR is between 1500-2000 ms.

2.6. Methodological Review of ^{1}H-MRS Studies in Extra-Temporal Lobe Epilepsy

In all patients in such studies (13 papers), no structural lesions were found on the MRI scans, but based on EEG the diagnosis was lateralized and localized in the parietal lobe or the frontal lobe and in two studies the occipital lobe (Table 2 # 7, 8).

All studies were conducted at 1.5 T [16, 46, 49-55] except four [4, 5, 29, 35]. Four of thirteen examinations used short TE in the range of 30-72 ms (Table 2 # 3, 9, 7, 8). All studies obtained spectra from the MRSI method except two of them (SVS with voxel size of 4×3.5×2.5 cm) (Table 2 # 7, 8).

2.7. Methodological Review of ^{1}H-MRS Studies in Generalized Epilepsy

All studies (13 papers) in this section examined subjects with IGE, including nine studies which examined JME patients [12, 14, 15, 56-61], three which examined Juvenile Absence Epilepsy (JAE) patients [15, 60, 62], and four which examined patients with Generalized Tonic-Clonic Seizures (GTCS) [12, 13, 15, 56].

There are some methodological differences in ^{1}H-MRS studies in generalized epilepsy studies. All studies were performed at 1.5 T, except two which used a 2 T scanner and a 3 T scanner [13, 59]. Two out of eleven studies used the STEAM sequence [56, 57], six used the MRSI technique and five studies obtained spectra from the SVS technique to examine patients. The values of TE and TR used here are: short TE: 30 and 80 ms, long TE: 135-272 ms, and TR: between 1000-6000 ms. Table 3 shows a comparison of methodological aspects in generalized epileptic patients. According to current knowledge, the most popular sequence for these studies is PRESS.

2.8. Review of Alterations of Neuro-metabolites in Patient with Epilepsy

The most important metabolite ratios in the study of TLE patients are NAA/Cr, NAA/Cr+Cho, and NAA/Cho [42, 63-85]. These three ratios decrease in the hippocampal and extra-hippocampal areas in TLE patients, which show neuronal loss or damage in that area, and may signify structural abnormality. In the second level, alterations of neuro-metabolite ratios are Cho/Cr [36, 65], (total N-acetyl aspartate) tNAA/Cr [39, 46, 86], tNAA/Cr+Cho, tNAA/mI [39], GABA plus homocarnosine (GABA+)/Cr [87], Glx/Cr [46, 87], NAA/mI, NAA/Glx [88], mI/Cr [22, 23]. Studies regarding ^{1}H-MRS in TLE patients with HS showed that there is a decrease in NAA and an increase in Cho, Cr, and mI concentrations ipsilateral to the seizure focus. Reduced hippocampal NAA and elevated Glx values have also been reported in MRI-negative patients [89-93].

The most common metabolite ratio in patients with ETLE is NAA/Cr (Table 2 # 1-6, 9-13). Other metabolite ratios in such patients are: Cho/Cr (Table 2 # 1, 5, 12, 13), NAA/Cho (Table 2 # 1, 6, 12, 13), NAA/Cr+Cho (Table 2 # 2, 12, 13), tNAA/Cr, Glx/mI and Glx/Cr (Table 2 # 7, 8), and Lac/Cr (Table 2 # 12). Reduced NAA/Cr or NAA/Cho ratios have been found in the seizure focus in FLE patients, which may help to lateralize the epileptogenic zone in MRI-negative FLE patients. Metabolic abnormalities in ^{1}H-MRS have also been identified in areas away from the seizure focus where there is no evidence of a lesion on MRI, and it is not clear whether this reflects widespread pathology without an MRI-evident lesion or a functional consequence of a seizure focus. tNAA, Glx, Cho, Cr, mI, GABA+, Lac concentrations in ETLE patients has been reported by R. J. Simister and his colleagues (Table 2 # 7, 8). In this study, IGE patients showed increased Glx and GABA+.

The NAA/Cr ratio is the most important neuro-metabolite ratio in patients with generalized epilepsy (Table 3 # 2-5, 9, 10). A. J. Ristić and colleagues reported Cho/tCr (Creatine-Phosphocreatine), NAA/tCr, NAA/Cho, and NAA/Cho+tCr ratios (Table 3 # 1). tNAA/Cr, Glx/tNAA, Glx/mI ratios have been reported by R. J. Simister and colleagues (Table 3 # 11). K. Lin and his colleagues reported Glx/Cr ratio (Table 3 # 5). Absolute neuro-metabolite concentrations in patients with generalized epilepsy are NAA (Table 3 # 6, 7, 9, 10), Cho (Table 3 # 6-8, 11), Cr (Table 3 # 6, 7), mI (Table 3 # 6-8, 11), tNAA, Glx, and Glu (Table 3 # 8, 11).

3. Correlations Studies

3.1. The Relationship between Histopathologic Finding and ^{1}H-MRS Alterations

MRS studies regarding histopathologic correlations in TLE showed that the observed NAA, NAA/Cr, tNAA, mI, NAA/Cho changes have a linear regression relationship with reduction in neuronal populations [31, 49, 94-96]. To address this, T. Hammen *et al*. studied 23 patients with unilateral TLE. They found a positive correlation between tNAA reduction and neuronal density in the dentate gyrus ($p=0.006$), hippocampal Cornu Ammonis (CA)1, CA3, and CA4 subfields ($p<0.001$, 0.015, 0.031, respectively) and a negative correlation between mI and neuronal loss in the hippocampal CA4 subfield ($p=0.028$) [95].

3.2.The Relationship between EEG Finding and ^{1}H-MRS Alterations

The results regarding correlations between the distribution of metabolic alterations and interracial EEG spikes showed a moderate level of concordance in the lateralization of TLE and ETLE patients [10, 44, 52, 53, 86, 97, 98]. T. Hammen *et al.* found that tNAA values and the degree of Interictal Epileptiform Discharges (IEDs) in EEG ($p=0.04$) have a negative correlation. However, there was a positive correlation between Cr and the duration of the seizure ($p=0.01$), which represents the relationship between the duration of the seizure and increased levels of Cr. The results of this study showed that the degree of tNAA reduction is probably indicative of neuronal dysfunction [86]. H. Aydin *et al.* also suggested the MRSI sensitivity index for lateralization in the left and right hippocampi, which were 100% and 92% respectively according to EEG findings [98].

3.3.The Relationship between Cognitive Performance and ^{1}H-MRS Alterations

The underlying pathology, seizures, medication, and IEDs are a number of factors that correlate with cognitive dysfunction in refractory TLE. Some studies have been carried out to investigate the correlation between memory function and ^{1}H-MRS findings and to characterize cognitive dysfunction in TLE patients with HS [25, 32, 64, 99-102]. To address this, M. A. Mantoan *et al.* assessed 29 patients and 24 controls and found a negative correlation between Intelligence Quotient (IQ), Rey Auditory Verbal Learning Test results, NAA/(Cho+Cr) ratio and epilepsy duration (r=0.551, p=0.031; r=0.585, p=0.022, r=0.569, p=0.027, respectively) in the left mesial temporal sclerosis group [101]. I. J. Namer *et al.* showed that there is no correlation between the NAA/(Cho+Cr) ratio or the T2 relaxation measurement alone and memory performances, whereas it has been declared that the combination of T2 relaxation time value and NAA can be used to examine the relationship between hippocampal dysfunction and memory performances before surgery for the evaluation of patients with TLE with MRI signs of HS [25].

3.4. The Relationship between MR Volumetry and ^{1}H-MRS Alterations

MR volumetry demonstrates volume loss in the hippocampus, which is an MRI abnormality in TLE patients with HS. Six studies investigated the relation between ^{1}H-MRS neuro-metabolites and MR volumetry in TLE patients with or without HS [9, 10, 32, 103-105]. E. Duzel *et al.* examined 22 patients with MR abnormality and normal MR. They found that hippocampal volumetry results did not correlate with the Apparent Diffusion Coefficient (ADC) value, NAA/(Cho+Cr), and the duration of the disease in any of the patients (with or without HS) or controls. There was a negative correlation between the NAA/(Cho+Cr) ratio and ADCs in the ipsilateral hippocampus (based on EEG recordings) and MR-positive patients (r= -0.45, p=0.05 and r= -0.94, p=0.001, respectively). In contrast, these two measurements did not have a significant correlation in patients without HS. According to the results, they suggested that these three techniques show the complementary aspects of hippocampal pathology [103]. G. Helms *et al.* examined 43 IGE patients and 38 healthy controls. They used the quantitative single voxel proton MR spectroscopy, thalamic volumetry, and Voxel Based Morphometry (VBM), to measure concentrations of Glx and NAA in the thalamus and occipital cortex, and fractions of thalamic grey and white matter. They found that quantitative ^{1}H-MRS and VBM provide further information for the involvement of the thalamus in the generation of seizures in IGE patients. The mean thalamic and cerebral volume was reduced in patients compared with controls (p=0.0001, p=0.0003, respectively) [106].

3.5. The Relationship between SPECT and PET results and ^{1}H-MRS Alterations

As mentioned above, currently, MRI, SPECT, and PET are the most important non-invasive methods for the detection of structural and functional abnormalities in TLE and ETLE patients. Decreased blood flow in the epileptogenic zone is detected by interracial SPECT and can aid in the lateralization of TLE patients with normal MRI, whereas it is less sensitive than PET [49, 97, 107, 108]. D. Lu *et al.* assessed the relationship between ^{1}H-MRS alterations (NAA reduction) and glucose metabolism in 12 patients with unilateral TLE (n=7 normal MRI and n=5 positive MRI). They found a positive correlation between the NAA/(Cho+Cr) ratio and glucose metabolism (r=0.54, p<0.01) [107]. Another study demonstrated the sensitivity of PET and ^{1}H-MRS (NAA/Cr and NAA/Cho ratios), which was 85% where the results were compared with MRI findings on only the ipsilateral side [108].

3.6. The Relationship between Clinical Characteristics of Epilepsy and ^{1}H-MRS Alterations

Some studies have examined the relationship between ^{1}H-MRS results and seizure frequency [4, 109]. In a study conducted by P. A. Garcia *et al.* there was a negative correlation between NAA concentration and seizure frequency in FLE and TLE patients (r=-0.72, p<0.02 and r=-0.60, p<0.06, respectively). However, the correlation between NAA/Cr ratio, FLE, TLE and the duration of epilepsy was poor (r=0.10, p<0.41 and r=0.18, p<0.34, respectively) [5].

4. Conclusion

Taking everything into consideration, there is methodological heterogeneity in applied methods (including CSI vs. SVS, MRS sequences, and their parameters) and the quantification methods. Nevertheless, increasing the field strength, improving RF pulse design methods, localization sequences, and post-processing and quantification procedures, especially at short TEs, can improve the overall diagnostic sensitivity and provide a valuable implication for epilepsy diagnosis in clinics. Mohammadi *et al*. suggested an interesting approach for the quantification of MRS data. They employed a dimension reduction technique for the spectral fitting of the MR spectroscopy data with short TE (=30 ms) and showed that the sensitivity and specificity of this modality in TLE patients are 60% and 82%, respectively. Overall, H. Aydin *et al*. suggested that proton MR spectroscopy imaging can be used for the lateralization of an epileptic focus in mTLE patients with 96% sensitivity (sensitivity in the right hippocampi was 92%) and 50% specificity.

Acknowledgements

This research has been supported by Tehran University of Medical Sciences & Health Services grant 94-02-30-29641.

References

1- Organisation, W.H., WHO Information Kit on Epilepsy What you can do. World Health Organization 2015. Available at: http://www.who.int/mental_health/neurology/epilepsy/information_kit_epilepsy/en/.

2- van Veenendaal, T.M., *et al.*, Metabolic and functional MR biomarkers of antiepileptic drug effectiveness: A review. *Neuroscience & Biobehavioral Reviews*, 2015. 59: p. 92-99.

3- Zhang, J., *et al.*, Multimodal neuroimaging in presurgical evaluation of drug-resistant epilepsy. *NeuroImage: Clinical*, 2014. 4: p. 35-44.

4- Garcia, P., *et al.*, Correlation of seizure frequency with N-acetyl-aspartate levels determined by 1 H magnetic resonance spectroscopic imaging. *Magnetic resonance imaging*, 1997. 15(4): p. 475-478.

5- Garcia, P.A., *et al*., Proton magnetic resonance spectroscopic imaging in patients with frontal lobe epilepsy. *Annals of Neurology*, 1995. 37(2): p. 279-281.

6- Chernov, M.F., *et al.*, Role of proton magnetic resonance spectroscopy in the preoperative evaluation of patients with mesial temporal lobe epilepsy. *J Neurol Sci*, 2009. 285(1-2): p. 212-9.

7- Duc, C.O., *et al.*, Quantitative 1 H MRS in the evaluation of mesial temporal lobe epilepsy in vivo. *Magnetic resonance imaging*, 1998. 16(8): p. 969-979.

8- Barker, P.B., *et al.*, Clinical MR Spectroscopy Techniques and Applications. 2009, New York: Cambridge University Press.

9- Kuzniecky, R., *et al.*, the Relative utility of ^{1}H spectroscopic imaging and hippocampal volumetry in the lateralization of mesial temporal lobe epilepsy. *Neurology*, 1998. 51(1): p. 66-71.

10- Cendes, F., *et al.*, Proton magnetic resonance spectroscopic imaging and magnetic resonance imaging volumetry in the lateralization of temporal lobe epilepsy: a series of 100 patients. Ann Neurol, 1997. 42(5): p. 737-46.

11- Campos, B.A.G., *et al.*, Proton MRS may predict AED response in patients with TLE. *Epilepsia*, 2010. 51(5): p. 783-788.

12- Bernasconi, A., *et al.*, Magnetic resonance spectroscopy and imaging of the thalamus in idiopathic generalized epilepsy. *Brain*, 2003. 126(11): p. 2447-2454.

13- Doelken, M.T., *et al.*, Multi-voxel magnetic resonance spectroscopy at 3 T in patients with idiopathic generalised epilepsy. *Seizure*, 2010. 19(8): p. 485-92.

14- Lin, K., *et al.*, Magnetic resonance spectroscopy reveals an epileptic network in juvenile myoclonic epilepsy. *Epilepsia*, 2009. 50(5): p. 1191-200.

15- Simister, R.J., *et al.*, Proton MRS reveals frontal lobe metabolite abnormalities in idiopathic generalized epilepsy. *Neurology*, 2003. 61(7): p. 897-902.

16- Simister, R.J., *et al.*, A proton magnetic resonance spectroscopy study of metabolites in the occipital lobes in epilepsy. *Epilepsia*, 2003. 44(4): p. 550-8.

17- Yahya, A., Metabolite detection by proton magnetic resonance spectroscopy using PRESS. *Progress in Nuclear Magnetic Resonance Spectroscopy*, 2009. 55(3): p. 183-198.

18-Moonen, C.T.W., *et al.*, Comparison of single-shot localization methods (steam and press) for In vivo proton NMR spectroscopy. *NMR in Biomedicine*, 1989. 2(5-6): p. 201-208.

19-Qi, J., *et al.*, MRI and ^{1}H-MRS detects volumetric and metabolic abnormalities of hippocampal sclerosis in temporal lobe epilepsy. *Journal of Nanjing Medical University*, 2007. 21(5): p. 333-336.

20-Hugg, J.W., et al., Neuron loss localizes human temporal lobe epilepsy by in vivo proton magnetic resonance spectroscopic imaging. *Ann Neurol*, 1993. 34(6): p. 788-94.

21-Choi, C.G. and J. Frahm, Localized proton MRS of the human hippocampus: metabolite concentrations and relaxation times. *Magn Reson Med*, 1999. 41(1): p. 204-7.

22-Shen, J., *et al.*, Use of short echo time two-dimensional ^{1}H-magnetic resonance spectroscopy in temporal lobe epilepsy with negative magnetic resonance imaging findings. *J Int Med Res*, 2009. 37(4): p. 1211-9.

23-Riederer, F., *et al.*, ^{1}H magnetic resonance spectroscopy at 3 T in cryptogenic and mesial temporal lobe epilepsy. *NMR Biomed*, 2006. 19(5): p. 544-53.

24-Riederer, F., *et al.*, Decrease of NAA with aging outside the seizure focus in mesial temporal lobe epilepsy—A proton-MRS study at 3 Tesla. *Brain research*, 2007. 1179: p. 131-139.

25-Namer, I.J., *et al.*, Combined measurements of hippocampal N-acetyl-aspartate and T2 relaxation time in the evaluation of mesial temporal lobe epilepsy: correlation with clinical severity and memory performances. *Epilepsia*, 1999. 40(10): p. 1424-32.

26-Fountas, K.N., *et al.*, Temporal pole proton preoperative magnetic resonance spectroscopy in patients undergoing surgery for mesial temporal sclerosis. *Neurosurg Focus*, 2012. 32(3): p. E3.

27-Briellmann, R.S., *et al.*, Hippocampal sclerosis: MR prediction of seizure intractability. *Epilepsia*, 2007. 48(2): p. 315-23.

28-Xu, M.Y., *et al.*, Proton MR Spectroscopy in Patients with Structural MRI-Negative Temporal Lobe Epilepsy. *J Neuroimaging*, 2015. 25(6): p. 1030-7.

29-Pan, J.W., *et al.*, Metabolic networks in epilepsy by MR spectroscopic imaging. *Acta Neurol Scand*, 2012. 126(6): p. 411-20.

30-Mueller, S.G., *et al.*, Widespread extrahippocampal NAA/(Cr+Cho) abnormalities in TLE with and without mesial temporal sclerosis. *J Neurol*, 2011. 258(4): p. 603-12.

31-Cohen-Gadol, A.A., *et al.*, Mesial temporal lobe epilepsy: a proton magnetic resonance spectroscopy study and a histopathological analysis. *J Neurosurg*, 2004. 101(4): p. 613-20.

32-Sawrie, S.M., *et al.*, Relationships among hippocampal volumetry, proton magnetic resonance spectroscopy, and verbal memory in temporal lobe epilepsy. *Epilepsia*, 2001. 42(11): p. 1403-7.

33-Hetherington, H., *et al.*, Proton nuclear magnetic resonance spectroscopic imaging of human temporal lobe epilepsy at 4.1 T. *Ann Neurol*, 1995. 38(3): p. 396-404.

34-Burneo, J.G., *et al.*, Chronic temporal lobe epilepsy: spatial extent and degree of metabolic dysfunction studied with magnetic resonance spectroscopy (MRS). *Epilepsy Res*, 2004. 62(2-3): p. 119-24.

35-Pan, J.W., *et al.*, 7T MR spectroscopic imaging in the localization of surgical epilepsy. *Epilepsia*, 2013. 54(9): p. 1668-78.

36-Mendes-Ribeiro, J.A., *et al.*, Reduction in temporal N-acetylaspartate and creatine (or choline) ratio in temporal lobe epilepsy: does this ^{1}H-magnetic resonance spectroscopy finding mean poor seizure control? *J Neurol Neurosurg Psychiatry*, 1998. 65(4): p. 518-22.

37-Chang, K.H., *et al.*, Usefulness of single-voxel proton MR spectroscopy in the evaluation of hippocampal sclerosis. *Korean J Radiol*, 2000. 1(1): p. 25-32.

38-McLean, M.A., *et al.*, Quantitative analysis of short echo time (1)H-MRSI of cerebral gray and white matter. *Magn Reson Med*, 2000. 44(3): p. 401-11.

39-Simister, R.J., *et al.*, A short-echo-time proton magnetic resonance spectroscopic imaging study of temporal lobe epilepsy. *Epilepsia*, 2002. 43(9): p. 1021-31.

40-Vermathen, P., *et al.*, Hippocampal structures: anteroposterior N-acetylaspartate differences in patients with epilepsy and control subjects as shown with proton MR spectroscopic imaging. *Radiology*, 2000. 214(2): p. 403-10.

41-Pan, J.W., *et al.*, Quantitative glutamate spectroscopic imaging of the human hippocampus. *NMR in biomedicine*, 2006. 19(2): p. 209-216.

42-Fadaie, F., *et al.*, ^{1}H-MRS metabolite's ratios show temporal alternation in temporal lobe seizure: Comparison between interictal and postictal phases. *Epilepsy Research*, 2016. 128: p. 158-162.

43-Flügel, D., *et al.*, Magnetisation transfer ratio of choline is reduced following epileptic seizures. *NMR in Biomedicine*, 2006. 19(2): p. 217-222.

44-Maton, B., *et al.*, Correlation of scalp EEG and ^{1}H-MRS metabolic abnormalities in temporal lobe epilepsy. *Epilepsia*, 2001. 42(3): p. 417-22.

45-Mueller, S.G., *et al.*, Proton magnetic resonance spectroscopy characteristics of focal cortical dysgenesis during status epilepticus and in the interictal state. *Seizure*, 2001. 10(7): p. 518-524.

46-Simister, R.J., *et al.*, The effect of epileptic seizures on proton MRS visible neurochemical concentrations. *Epilepsy Res*, 2008. 81(1): p. 36-43.

47-Wellard, R.M., *et al.*, Myoinositol Abnormalities in Temporal Lobe Epilepsy. *Epilepsia*, 2003. 44(6): p. 815-821.

48-Mohammadi, N., *et al*., A Novel ^{1}H-MRS Quantification Approach Based on Spectral Fitting for Lateralization/Localization of Seizure Foci in Patients with Temporal Lobe Epilepsy. *Frontiers in Biomedical Technologies*, 2015. 2(1): p. 8-14.

49-Krsek, P., *et al.*, (1)H MR spectroscopic imaging in patients with MRI-negative extratemporal epilepsy: correlation with ictal onset zone and histopathology. *Eur Radiol*, 2007. 17(8): p. 2126-35.

50-Guye, M., *et al.*, ^{1}H-MRS imaging in intractable frontal lobe epilepsies characterized by depth electrode recording. *NeuroImage*, 2005. 26(4): p. 1174-1183.

51-Mueller, S.G., *et al.*, Identification of the epileptogenic lobe in neocortical epilepsy with proton MR spectroscopic imaging. *Epilepsia*, 2004. 45(12): p. 1580-9.

52-Serles, W., *et al.*, Relation of interictal spike frequency to ^{1}H-MRSI-measured NAA/Cr. *Epilepsia*, 1999. 40(12): p. 1821-7.

53-Stanley, J.A., *et al.*, Proton magnetic resonance spectroscopic imaging in patients with extratemporal epilepsy. *Epilepsia*, 1998. 39(3): p. 267-73.

54-Li, L.M., *et al.*, Spatial extent of neuronal metabolic dysfunction measured by proton MR spectroscopic imaging in patients with localization-related epilepsy. *Epilepsia*, 2000. 41(6): p. 666-74.

55-Leite, R.A., *et al.*, Proton magnetic spectroscopy agreed better with magnetic resonance image to lateralization of the epileptogenic zone than with surface electroencephalography. *Arq Neuropsiquiatr*, 2013. 71(9A): p. 584-90.

56-Savic, I., Y. Österman, and G. Helms, MRS shows syndrome differentiated metabolite changes in human-generalized epilepsies. *NeuroImage*, 2004. 21(1): p. 163-172.

57-Savic, I., *et al.*, MR spectroscopy shows reduced frontal lobe concentrations of N-acetyl aspartate in patients with juvenile myoclonic epilepsy. *Epilepsia*, 2000. 41(3): p. 290-6.

58-Ristić, A.J., *et al.*, Hippocampal metabolic dysfunction in juvenile myoclonic epilepsy: 3D multivoxel spectroscopy study. *Journal of the Neurological Sciences*, 2011. 305(1–2): p. 139-142.

59-Mory, S.B., *et al.*, Thalamic dysfunction in juvenile myoclonic epilepsy: a proton MRS study. *Epilepsia*, 2003. 44(11): p. 1402-5.

60-Kabay, S.C., *et al.*, A proton magnetic resonance spectroscopic study in juvenile absence epilepsy in early stages. *Eur J Paediatr Neurol*, 2010. 14(3): p. 224-8.

61-Haki, C., *et al.*, Proton magnetic resonance spectroscopy study of bilateral thalamus in juvenile myoclonic epilepsy. *Seizure*, 2007. 16(4): p. 287-295.

62-Fojtikova, D., *et al.*, Magnetic resonance spectroscopy of the thalamus in patients with typical absence epilepsy. *Seizure*, 2006. 15(7): p. 533-40.

63-Brázdil, M., *et al.*, Correlation study of optimized voxel-based morphometry and ^{1}H MRS in patients with mesial temporal lobe epilepsy and hippocampal sclerosis. *Human Brain Mapping*, 2009. 30(4): p. 1226-1235.

64-Hanoglu, L., *et al.*, Correlation between ^{1}H MRS and memory before and after surgery in mesial temporal lobe epilepsy with hippocampal sclerosis. *Epilepsia*, 2004. 45(6): p. 632-40.

65-Achten, E., *et al.*, Value of single-voxel proton MR spectroscopy in temporal lobe epilepsy. *AJNR Am J Neuroradiol*, 1997. 18(6): p. 1131-9.

66-Achten, E., *et al.*, Single-voxel proton MR spectroscopy and positron emission tomography for lateralization of

refractory temporal lobe epilepsy. *AJNR Am J Neuroradiol*, 1998. 19(1): p. 1-8.

67-Lantz, G., M. Seeck, and F. Lazeyras, Extent of preoperative abnormalities and focus lateralization predict postoperative normalization of contralateral ^{1}H-magnetic resonance spectroscopy metabolite levels in patients with temporal lobe epilepsy. *AJNR Am J Neuroradiol*, 2006. 27(8): p. 1766-9.

68-Capizzano, A.A., *et al.*, Multisection proton MR spectroscopy for mesial temporal lobe epilepsy. *AJNR Am J Neuroradiol*, 2002. 23(8): p. 1359-68.

69-Vermathen, P., *et al.*, Evidence of neuronal injury outside the medial temporal lobe in temporal lobe epilepsy: N-acetylaspartate concentration reductions detected with multisection proton MR spectroscopic imaging--initial experience. *Radiology*, 2003. 226(1): p. 195-202.

70-Ng, T.C., *et al.*, Temporal lobe epilepsy: presurgical localization with proton chemical shift imaging. *Radiology*, 1994. 193(2): p. 465-72.

71-Zubler, F., *et al.*, Contralateral medial temporal lobe damage in right but not left temporal lobe epilepsy: a ^{1}H magnetic resonance spectroscopy study. Journal of Neurology, *Neurosurgery & Psychiatry*, 2003. 74(9): p. 1240-1244.

72-Spencer, D.C., *et al*., Temporal lobe magnetic resonance spectroscopic imaging following selective amygdalohippocampectomy for treatment-resistant epilepsy. *Acta Neurol Scand*, 2005. 112(1): p. 6-12.

73-Shih, J.J., *et al.*, Magnetoencephalographic and magnetic resonance spectroscopy evidence of regional functional abnormality in mesial temporal lobe epilepsy. *Brain Topogr*, 2011. 23(4): p. 368-74.

74-Shih, J.J., *et al*., Areas of interictal spiking are associated with metabolic dysfunction in MRI-negative temporal lobe epilepsy. *Epilepsia*, 2004. 45(3): p. 223-9.

75-Lee, S.K., *et al.*, Effect of seizure on the hippocampus in mesial temporal lobe epilepsy and neocortical epilepsy: an MRS study. *Neuroradiology*, 2005. 47(12): p. 916-23.

76-Hammen, T., *et al.*, ^{1}H-MR spectroscopy: a promising method in distinguishing subgroups in temporal lobe epilepsy? *J Neurol Sci*, 2003. 215(1-2): p. 21-5.

77-Cendes, F., *et al.*, Lateralization of temporal lobe epilepsy based on regional metabolic abnormalities in proton magnetic resonance spectroscopic images. *Ann Neurol*, 1994. 35(2): p. 211-6.

78-Li, L.M., et al., Proton Magnetic Resonance Spectroscopic Imaging Studies in Patients with Newly Diagnosed Partial Epilepsy. *Epilepsia*, 2000. 41(7): p. 825-831.

79-Obata, T., *et al.*, Neural damage due to temporal lobe epilepsy: dual-nuclei (proton and phosphorus) magnetic resonance spectroscopy study. *Psychiatry Clin Neurosci*, 2004. 58(1): p. 48-53.

80-Guye, M., *et al.*, Metabolic and electrophysiological alterations in subtypes of temporal lobe epilepsy: a combined proton magnetic resonance spectroscopic imaging and depth electrodes study. *Epilepsia*, 2002. 43(10): p. 1197-209.

81-Meyer, P., *et al.*, Inter-modality comparisons of seizure focus lateralization in complex partial seizures. *European Journal of Nuclear Medicine*, 2001. 28(10): p. 1529-1540.

82-Castillo, M., J.K. Smith, and L. Kwock, Proton MR Spectroscopy in Patients with Acute Temporal Lobe Seizures. *AJNR Am J Neuroradiol*, 2001. 22: p. 152-157.

83-Zhang, J., *et al.*, Identifying the affected hemisphere with a multimodal approach in MRI-positive or negative, unilateral or bilateral temporal lobe epilepsy. *Neuropsychiatr Dis Treat*, 2014. 10: p. 71-81.

84-Fojtikova, D., *et al*., Magnetic resonance spectroscopy of the thalamus in patients with mesial temporal lobe epilepsy and hippocampal sclerosis. *Epileptic Disord*, 2007. 9 Suppl 1: p. S59-67.

85-Ende, G.R., *et al.*, Temporal lobe epilepsy: bilateral hippocampal metabolite changes revealed at proton MR spectroscopic imaging. *Radiology*, 1997. 202(3): p. 809-17.

86-Hammen, T., *et al.*, ^{1}H-MR spectroscopy indicates severity markers in temporal lobe epilepsy: correlations between metabolic alterations, seizures, and epileptic discharges in EEG. *Epilepsia*, 2007. 48(2): p. 263-9.

87-Simister, R.J., *et al.*, Proton MR spectroscopy of metabolite concentrations in temporal lobe epilepsy and the effect of temporal lobe resection. *Epilepsy Res*, 2009. 83(2-3): p. 168-76.

88-Woermann, F.G., *et al*., Short echo time single-voxel ^{1}H magnetic resonance spectroscopy in magnetic resonance imaging-negative temporal lobe epilepsy: different biochemical profile compared with hippocampal sclerosis. *Ann Neurol*, 1999. 45(3): p. 369-76.

89- Capizzano, A.A., *et al.*, Temporal lobe epilepsy: a qualitative reading of ^{1}H MR spectroscopic images for presurgical evaluation. *Radiology*, 2001. 218(1): p. 144-51.

90- Connelly, A., *et al.*, Proton magnetic resonance spectroscopy in MRI-negative temporal lobe epilepsy. *Neurology*, 1998. 51(1): p. 61-66.

91- Doelken, M.T., *et al.*, (1)H-MRS profile in MRI positive- versus MRI negative patients with temporal lobe epilepsy. *Seizure*, 2008. 17(6): p. 490-7.

92- Hammen, T., *et al.*, Identifying the affected hemisphere by (1)H-MR spectroscopy in patients with temporal lobe epilepsy and no pathological findings in high-resolution MRI. *Eur J Neurol*, 2006. 13(5): p. 482-90.

93- Vermathen, P., *et al.*, Temporal lobectomy for epilepsy: recovery of the contralateral hippocampus measured by (1)H MRS. *Neurology*, 2002. 59(4): p. 633-6.

94- Meiners, L.C., *et al.*, Proton magnetic resonance spectroscopy of temporal lobe white matter in patients with histologically proven hippocampal sclerosis. *J Magn Reson Imaging*, 2000. 11(1): p. 25-31.

95- Hammen, T., *et al.*, Non-invasive detection of hippocampal sclerosis: correlation between metabolite alterations detected by (1)H-MRS and neuropathology. *NMR Biomed*, 2008. 21(6): p. 545-52.

96- Stefan, H., *et al.*, Magnetic Resonance Spectroscopy and Histopathological Findings in Temporal Lobe Epilepsy. *Epilepsia*, 2001. 42(1): p. 41-46.

97- Doelken, M.T., *et al.*, Multimodal coregistration in patients with temporal lobe epilepsy--results of different imaging modalities in lateralization of the affected hemisphere in MR imaging positive and negative subgroups. *AJNR Am J Neuroradiol*, 2007. 28(3): p. 449-54.

98- Aydin, H., *et al.*, Value of Proton-MR-Spectroscopy in the Diagnosis of Temporal Lobe Epilepsy; Correlation of Metabolite Alterations With Electroencephalography. *Iran J Radiol*, 2012. 9(1): p. 1-11.

99- Pauli, E., *et al.*, Chemical Shift Imaging Spectroscopy and Memory Function in Temporal Lobe Epilepsy. *Epilepsia*, 2000. 41(3): p. 282-289.

100- Kikuchi, S., *et al.*, A study of the relationship between metabolism using ^{1}H-MRS and function using several neuropsychological tests in temporal lobe epilepsy. *Seizure*, 2001. 10(3): p. 188-93.

101- Mantoan, M.A., *et al.*, Correlation between memory, proton magnetic resonance spectroscopy, and interictal epileptiform discharges in temporal lobe epilepsy related to mesial temporal sclerosis. *Epilepsy Behav*, 2009. 16(3): p. 447-53.

102- Incisa della Rocchetta, A., *et al.*, Verbal memory impairment after right temporal lobe surgery: role of contralateral damage as revealed by ^{1}H magnetic resonance spectroscopy and T2 relaxometry. *Neurology*, 1995. 45(4): p. 797-802.

103- Düzel, E., *et al*., Measures of hippocampal volumes, diffusion and ^{1}H MRS metabolic abnormalities in temporal lobe epilepsy provide partially complementary information. *European Journal of Neurology*, 2004. 11(3): p. 195-205.

104- Cendes, F., *et al.*, Proton magnetic resonance spectroscopic images and MRI volumetric studies for lateralization of temporal lobe epilepsy. *Magn Reson Imaging*, 1995. 13(8): p. 1187-91.

105- Bernasconi, A., *et al.*, EEG background delta activity in temporal lobe epilepsy: correlation with volumetric and spectroscopic imaging. *Epilepsia*, 1999. 40(11): p. 1580-6.

106- Helms, G., *et al.*, Increased thalamus levels of glutamate and glutamine (Glx) in patients with idiopathic generalised epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry*, 2006. 77(4): p. 489-494.

107- Lu, D., *et al*., Temporal lobe epilepsy: correlation of proton magnetic resonance spectroscopy and 18F-fluorodeoxyglucose positron emission tomography. *Magn Reson Med*, 1997. 37(1): p. 18-23.

108- Park, S.W., *et al*., Lateralizing ability of single-voxel proton MR spectroscopy in hippocampal sclerosis: comparison with MR imaging and positron emission tomography. *AJNR Am J Neuroradiol*, 2001. 22(4): p. 625-31.

109- Someya, Y., *et al*., Seizure frequency and bilateral temporal abnormalities: a proton magnetic resonance spectroscopy of temporal lobe epilepsy. *Seizure - European Journal of Epilepsy*, 2000. 9(4): p. 274-279.