Additional value of Magnetic Resonance Spectroscopy for epilepsy diagnostics in the normal appearing epileptogenic zone

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ABSTRACT

Epilepsy affects 50 million people worldwide approximately, thus it is considered one of the most common neurological diseases. For this reason, a reliable diagnosis is of paramount importance. Neuroimaging plays an essential role in the evaluation. Although CT scans are typically the first modality used to detect the underlying cause of an epileptic seizure, they are likely to miss the majority of the epileptogenic lesions. Therefore, other imaging modalities are used to detect the cause of epilepsy. MRI is generally performed; however, it only identifies structural pathology in the epileptic brain in one third of the epileptic patients. For that reason, MRS is a promising tool in the detection of the normal appearing epileptogenic zone. This modality detects abnormalities that are invisible to a conventional MRI because metabolic abnormalities often precede structural changes.

TLE is the most common form of focal epilepsy in which about 20% of patients have negative structural MR images. The majority of the reviewed studies confirm that NAA, Cr and Cho are the most commonly used metabolites to identify the epileptogenic zone in MRI negative TLE and ETLE. Moreover, NAA/Cr, NAA/Cho and NAA/(Cr+Cho) are the most widely accepted ratios for lateralization of the normal appearing epileptogenic zone. Furthermore, NAA and MI have been reported as the metabolites that best enable the study of seizure spread.

I. INTRODUCTION

A. Epilepsy

According to the International League Against Epilepsy (ILAE), epilepsy is a disease in which three conditions have to be met: at least two unprovoked seizures occurring more than 24 hours apart; one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and diagnosis of an epilepsy syndrome. This definition was codified in 2014, after modifying the previous from 2005 [1].

Also, as defined by the ILAE, an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [2].

i. Pathophysiology

The aetiology of epilepsy depends on the age groups, as shown in figure 1. While in children the most common causes of seizures are genetic, injury due to perinatal insults and malformations of cortical development; in adults the causes are encephalitis/meningitis, traumatic brain injury, brain tumours and strokes [3] [4] [5] [6].

The displayed pie charts were created from data in two studies evaluating aetiologies of epilepsy in childhood [7] and adults [8].

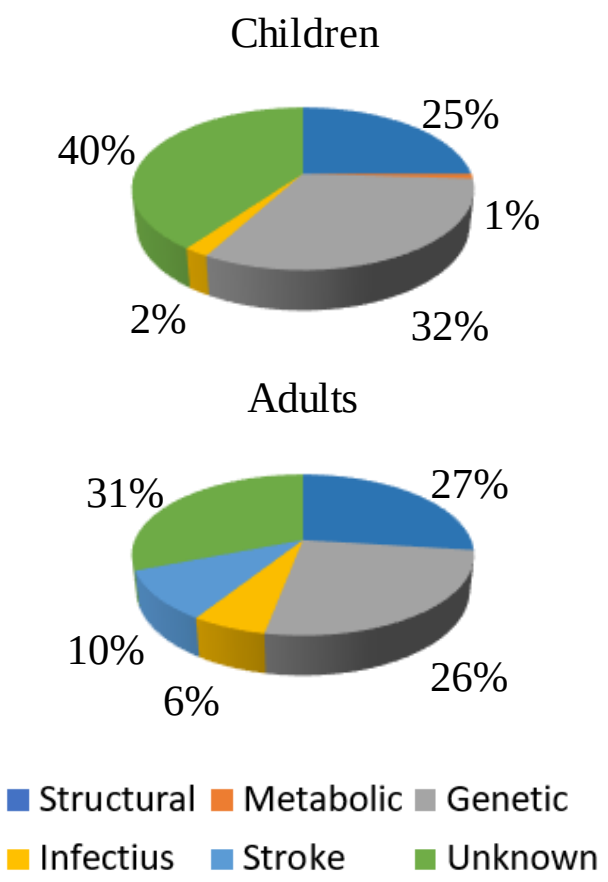

Figure 1. Aetiologies of epilepsy by age using the ILAE classification of epilepsies

ii. Epidemiology

As reported by the World Health Organization (WHO), epilepsy affects 50 million people worldwide approximately, thus it is considered one of the most common neurological diseases [9].

On the one hand, the incidence of epilepsy is 50.4 to 81.7 per 100,000 people per year [10]. On the other hand, the raw global prevalence of lifetime epilepsy is 1099 per 100,000 people, whereas active epilepsy prevalence is 690 per 100,000 people [11]. In the following years, the prevalence will increase because people are now living longer with brain tumours and the actual survival rate for severe head injuries, strokes and intracranial infections is higher.

As shown in figure 2, the highest prevalences are found in Africa and Latin America, although the highest incidences are reported in the Middle East and Latin America. These regions are primarily low and middle income countries; as expected, the highest disease burden falls disproportionately on regions with the fewest healthcare resources.

Figure 2. World map of the prevalence and incidence of epilepsy by WHO regions. Source: (Vaughan et al., 2019). Published with permission. Map generated by ©OpenStreetMap contributors (http://www.openstreetmap.org/copyright)

iii. Classification

The classification of seizures, epilepsies, and epilepsy syndromes has evolved over the years. The correct understanding is of great importance in the diagnosis and treatment of seizures and epilepsies.

In 2017 the ILAE published an operational classification of seizures and epilepsies. Two different versions of seizure classification were created: basic and expanded, as displayed in figures 3 and 4, respectively [12] [13] [14].

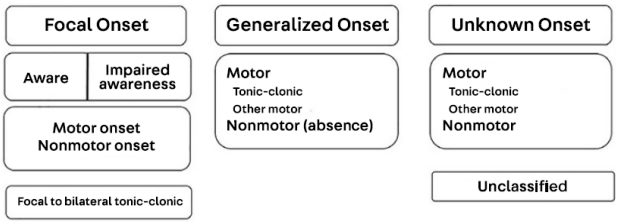

Figure 3. Basic version of 2017 ILAE seizure type classification. Source: (Fisher et al., 2017). Published with permission

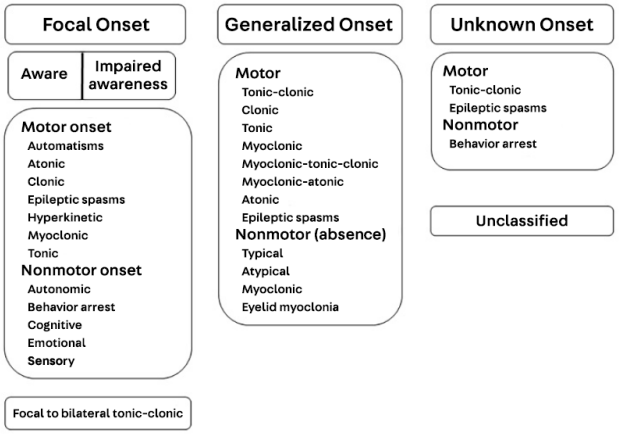

Figure 4. Expanded version of 2017 ILAE seizure type classification. Source: (Fisher et al., 2017). Published with permission

Similar to seizure classification, the epilepsies are classified as generalized or focal. Additionally, there are two other categories: combined generalized and focal epilepsy and unknown epilepsy [15].

Finally, a new addition to the current classification system is the epilepsy syndrome classification, defined as "a cluster of features incorporating seizure types, EEG and imaging features that tend to occur together" [15]. The ILAE has never formally classified a list of epilepsy syndromes; however, well-known and accepted syndromes are described.

iv. Epileptogenic Lesion And Related Areas

Figure 5 displays the topographic relation of the epileptogenic lesion identified by MRI with the results of other localizing diagnostic methods such as EEG-video monitoring, PET and SPECT. There is a close relationship between these areas, which may also include remote regions, as shown for the irritative zone.

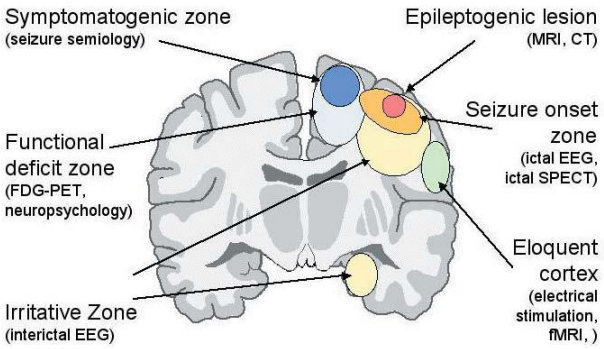

Figure 5. Topographic relation of the epileptogenic lesion with the results of other localizing diagnostic methods. Source: (Vollmar et al., 2004). Published with permission

Epileptogenic Lesion

Structural lesions causing epilepsies are called epileptogenic lesions. The generator of the epileptic activity is not the lesion itself but the effect it has on adjacent neurons [16].

Irritative Zone

The irritative zone is defined as the area generating interictal epileptiform discharges which are recorded on EEG [17].

Seizure Onset Zone

The seizure onset zone is the cortical area from which the patient's habitual seizures originate [17].

Symptomatogenic Zone

Epileptic activity will only lead to clinical signs and symptoms if symptomatogenic cortex is involved in the epileptic activity [17].

Functional Deficit Zone

The functional deficit zone defines the areas of cortical dysfunction in the interictal state [17].

Epileptogenic Zone

The epileptogenic zone is defined as the cortical area, whose complete removal is necessary and sufficient to achieve seizure freedom [17].

B. Neuroimaging Procedures

The majority of epilepsy patients presenting a first epileptic seizure undergo neuroimaging procedures. Neuroimaging plays an essential role in two settings: in patients with a first seizure and in patients with chronic medically refractory focal epilepsies [17].

In the first situation, neuroimaging is mainly performed to detect the underlying causes that require immediate treatment. CT scans are typically the first modality used, since they are more readily available in emergency situations. However, CT is likely to miss the majority of epileptogenic lesions. Therefore, other imaging modalities are used to detect the cause of epilepsy [17].

i. Imaging modalities

Structural Magnetic Resonance Imaging (MRI)

Although the percentage of patients with lesions identified by MRI continues to increase because of the improvements in image acquisition and data processing made in recent years [17], MRI only identifies structural pathology in the epileptic brain in one third of the epileptic patients [18] [19] [20] [21].

In 2013, O'Brien et al. [18] reported that potentially epileptogenic lesions were detected in 177 from the 764 acquired MRI scans, which it is just the 23% of all the cases. More recent studies show the increase in lesions identified by MRI mentioned above. Davagnanam et al. [19] found out that more than one third of people with chronic epilepsy in rural China have potentially epileptogenic lesions identifiable on brain MRI. Likewise, Samia et al. [20] concluded that up to a third of the children who underwent an MRI had a positive yield for abnormal findings. Furthermore, Hainc et al. [21] described that 262 patients were MRI negative from a total of 738.

Functional Magnetic Resonance Imaging (fMRI)

fMRI measures regional cerebral blood. It is used to localize eloquent areas in patients being considered for resective epilepsy surgery and in whom the epileptogenic zones are adjacent to eloquent cortex [17].

Magnetic Resonance Spectroscopy (MRS)

MRS allows the in vivo quantification of different cerebral metabolites. The spectroscopic pattern of a reduced ratio of NAA/(Cr+Cho) has a high sensitivity for the detection of the epileptogenic focus [17].

Diffusion Tensor Imaging (DTI)

DTI visualizes the primary orientation of fiber tracks. As reported by Assaf et al. [22], DTI revealed an area of histopathologically confirmed gliosis not visible in structural MRI, including FLAIR sequences.

Nuclear Medicine Imaging (NMI)

NMI is based on the detection of radiation, emitted from previously injected radiopharmaceuticals. Radioactive labelling of specific tracer molecules allows the qualitative and quantitative analysis of different physiological parameters such as glucose metabolism [17].

Positron-emission tomography (PET)

PET uses positron-emitting radionuclides such as 18-F, 11-C or 15-O for the radioactive labelling of organic molecules. As shown in Engel et al. [23], visualization of the cerebral glucose metabolism using 18-F-fluoro-deoxy-glucose is an established tool for localizing the epileptogenic region. Moreover, Arnold et al. [24] reported that PET with 11C-labelled flumazenil reveals a reduced GABA-A receptor density in the epileptogenic region.

Single Photon Emission Computed Tomography (SPECT)

Epileptic activity is associated with changes in regional cerebral blood flow that can be visualized with SPECT images. Usually, technetium-99m-labelled ethyl cysteinate dimer or hexamethyl propylene aminoxime are used as radiotracers [17].

However, both PET and SPECT have been discouraged as they are expensive, need exposure to radiation and utilize radioactive contrast agents [25].

C. Goal

In this review the focus will be on the assessment of the normal appearing epileptogenic zone with MRS. The available literature on the use of MRS in the identification and lateralization of the epileptogenic zone in patients with negative structural MR images will be evaluated. Also, the study of seizure spread with MRS and its relationship to age are aimed to be addressed in this work.

In order to provide a more detailed review, the study of epilepsy is divided into two different groups. Firstly, Temporal Lobe Epilepsy (TLE) and secondly, Extratemporal Lobe Epilepsy (ETLE) are tackled.

II. METHODS

This literature research has been conducted mainly with libraries such as PubMed, NCBI, Google Scholar and Wiley Online Library, which are the most commonly used source libraries in the biomedical field.

Articles with a main focus on visible MRI epilepsy and other imaging modalities other than MRS were excluded to keep the focus on the use of MRS in epileptic patients with negative structural MR images. Thus, the search terms in this study were "epilepsy", "TLE" "ETLE", "MRI-negative" and "MRS", among others.

In order to be part of the review, a paper had to be published in or after January 2013; although occasionally a slightly older source has been used to explain details of epilepsy pathology, which has not changed since then, or to compare it with recent studies.

III. MAGNETIC RESONANCE SPECTROSCOPY (MRS)

A. Definition

In vivo MRS enables non-invasive measurements of the chemical composition of living tissue. Although there are many nuclear MR-visible nuclei, ^{1}H spectroscopy is the most widely used because of its high sensitivity and its wealth of information content [26].

^{1}H MRS measures the chemical composition of the brain by harnessing signals from spinning hydrogen protons. Following exposure to an external magnetic field, protons in different molecules spin at different frequencies; this generates each molecule's unique chemical fingerprint on the metabolite spectrum in parts per million [27] [28] [29].

The information available from MRS complements the detailed structural information that is provided by conventional MRI. MRS makes possible to lateralize the epileptogenic focus, to diagnose the underlying nature of an epileptogenic lesion, to define the extent of a surgical resection and to predict postoperative outcome. Therefore, MRS has been used in the clinic to localize the seizure focus on patients without obvious MR abnormalities (MR-negative epilepsy) [26].

MRS detects abnormalities that are invisible to a conventional MRI because metabolic abnormalities often precede structural changes [30]. However, it should be noted that the connection between the severity of metabolic disturbance and structural lesion is not straightforward [31].

B. Single-Voxel vs Chemical Shift Imaging

Two different types of MRS acquisition can be performed: single-voxel or chemical shift imaging (CSI). On the one hand, single-voxel MRS measures the MR signal of a single selected region of interest whereas signal outside this area is suppressed. On the other hand, 2-D or 3-D CSI obtains information from different parts of the brain and allows retrospective assessment of regions of interest [32].

Single-voxel spectroscopy includes short acquisitions, explicit spatial localization, homogeneous shimming and good water suppression. Moreover, it is easy to interpret, provides high quality spectra and avoids time-consuming post-processing. Nonetheless, CSI has the advantage of obtaining multiple spectra simultaneously during one measurement [32].

Furthermore, the single-voxel approach requires a priori hypothesis of the epileptogenic focus, which limits its ability to provide help in MRI-negative patients with unclear seizure onset [33].

C. Metabolites In Epilepsy

The most important metabolites in MRS to detect epilepsy are:

- **N-acetyl-aspartate (NAA)** is a marker for neural status and integrity, in particular for neural mitochondrial metabolism.
- **Creatine (Cr)** is a marker for intracellular metabolism.
- **Choline (Cho)** is a marker for membrane integrity and turnover (oligodendroglia or myelination).
- **Myo-inositol(MI)** is a marker for glial cell integrity.
- **Glutamate and glutamine (Glx)** are the major excitatory neurotransmitters in the central nervous system, which play a role in mitochondrial metabolism and can serve as a marker of epileptic networks.
- **ɤ-amino-butyric acid (GABA)** is the major inhibitor neurotransmitter in the central nervous system.
- **Lactate (Lac)** is a marker for seizure-induced neuronal damage.

D. Temporal Lobe Epilepsy

The temporal lobe is the most epileptogenic region of the brain, making TLE the most common form of focal epilepsy [34] [32]. It is less frequently encountered in children compared to adults [32].

About 20% of patients with TLE have negative structural MR images [36]. Therefore, MRS is a promising tool for assessing patients with epilepsy. It offers increased sensitivity to detect temporal pathology that is not obvious on structural MR scans [37].

So far, the research on MRS in epilepsy has focused on 3 areas: identification of the epileptogenic zone, lateralization of the epileptogenic zone and study of the seizure spread.

Identifying and lateralizing the seizure focus with a non-invasive study is crucial for a good surgical resection outcome in drug-resistant patients. Otherwise, invasive studies or additional surgeries for placement of intracranial electrodes, which may have potential risks, would have to be carried out [37].

Moreover, studying the seizure spread is of vital importance since greater and faster seizure spread is associated with higher surgical failure [38].

Each of these areas is discussed below and the most important details regarding the type of MRS acquisition, the metabolites studied in each case and their change are presented in table 1.

i. Identification Epileptogenic Zone

For more than two decades, reports on MRS have noted that it is a promising neuroimaging modality. Most MRS studies in patients with TLE have shown a decrease in NAA, Cr, Cho, NAA/Cr, NAA/Cho and NAA/(Cr+Cho) in the epileptogenic zone.

Early studies reviewed typical findings on MRS and its major applications in epilepsy [17] [26]. As reported by Kuzniecky et al. [26], a focal reduction of NAA and an increase of Cho in patients with non-lesional TLE with good correlation with EEG (“gold standard”) abnormalities and severity of cell loss was found. Also, Cendes et al. [39] stated that reduced unilateral NAA/(Cr+Cho) on the side of EEG seizure onset could be identified in the majority of cases.

However, a linear correlation between this ratio reduction and hippocampal volume loss measured by volumetry was not found [40]. This demonstrates that NAA/(Cr+Cho) reduction does not necessarily reflect neuronal loss, but it is an effect of neuronal dysfunction which precedes cell loss and volume reduction.

In line with this finding, Hajek et al. [41] described a decrease in NAA, but a straightforward correlation between NAA concentrations and the extent of neuronal loss could not be found [42] [43]. Moreover, detailed analysis of metabolite concentration in hippocampal subfields in Hippocampal Sclerosis (HS) using high-resolution MRS of tissue extracts confirmed that the loss of neurons does not simply mean a decreased production of NAA [44].

Miller et al. [32] reviewed a decrease in NAA/Cr, NAA/Cho and NAA/(Cr+Cho) [45] [46] [47] [48]. Nonetheless, this time the reduction of NAA was correlated with neural cell loss and reactive

astrogliosis in HS. In this revision it was also stated that changes in NAA are not limited to chronic seizures [49] [50], since reduced NAA has also been observed in newly diagnosed TLE [51]. Furthermore, an increase in MI as a consequence of induction of Na^+/MI cotransporter following seizure activity in the epileptogenic zone was reported [52].

The same year, Oz et al. [28] documented abnormalities in NAA concentration and the NAA/Cr ratio have been useful for detecting injured brain in the seizure onset focus. Moreover, MRS measures were extended to neurotransmitters, for instance, to assess GABA in patients with epilepsy at ultrahigh field strengths.

Likewise, Aun et al. [34] evaluated the role of MRS in non-lesional TLE. Decreased NAA and increased Cr and Cho were helpful in the identification of the seizure focus on refractory focal epilepsy patients. While the loss of NAA signals is consistent with neuronal loss or damage, the basis for the increase in the Cho and Cr signals remains unclear. One possible explanation is provided by the study of neuronal cells, which showed that the concentrations of Cho and Cr are much higher in astrocyte and oligodendrocyte preparations than in cerebellar granule neurons. It may be that the changes in Cho and Cr reflect reactive astrocytosis.

Doelken et al. [31] pioneered the study that highlights a clear "NAA cut-off" in the hippocampi between MRI positive and MRI negative TLE patients and healthy controls. The highest degree of NAA reduction compared to healthy controls was seen in the MRI positive group. A moderate but still significant reduction of NAA was noticed in the MRI negative group. The minor degree of NAA reduction in the MRI negative group may be attributed to a minor lesion of unknown underlying cause, respectively initial disease stage.

Along the same lines, Woermann et al. [53] reported that the decrease of NAA was less marked in MRI negative hippocampus than in MRI positive hippocampus on the seizure side.

Nicolo et al. [54] investigated the role of MRS in studying glutamate as a biomarker for post-stroke epilepsy. The regional increases in Glx may be the result of hyperexcitability [55]. Additionally, in an MRS study of focal cortical dysplasia, patients had elevated levels of Glx compared with controls [56]. Besides, Savic et al. reported that Glx/NAA and Glx/Cho ratios can correctly identify the epileptogenic zone in patients with TLE [57].

Sharma et al. [33] studied how chronic, low-level neuroinflammation underlies epileptogenesis. Decreased NAA and increased Cr and MI enabled localizing epileptogenic onset zone, especially in those patients who were treatment-resistant and considered MRI-negative.

Recently, Mohamed et al. [35] carried out a study to recognize the epileptogenic zone in patients with non-lesional Focal Impaired Awareness Epilepsy (FIAE) by evaluating the cerebral metabolic alterations using MRS. The relative concentrations ratios of NAA/Cr, NAA/Cho, NAA/(Cr+Cho), MI/NAA, Glx/NAA and Glx/Cr were taken as analysis indices. They were bilaterally measured in all pairs of selected voxels of interest (VOIs).

In accordance with previous studies [31] [31] [58], the means of NAA/Cho, NAA/Cr and NAA/(Cr+Cho) peak ratios were significantly reduced; while, according to other studies [57] [59] [60], each of the MI/NAA, Glx/NAA and Glx/Cr was significantly increased in the suggested zones of epileptogenic activity, when compared to the corresponding regions without epileptogenic activity on the contralateral hemisphere.

Nonetheless, Davis et al. [59] observed elevated NAA/Cr in the epileptogenic focus when compared to the corresponding contralateral region and Hammena et al. [61] reported an increase in the Glx concentration contralateral to the epileptogenic focus in patients with MRI negative results and postulated a possible neuronal damage contralateral to epileptogenic focus.

Many previous studies that support the hypothesis of increased glutamate level in the epileptogenic zone assume that elevated glutamate level within the glial-neuronal unit is a key sign of both mitochondrial and metabolic injury induced by the hyper-excitable state that characterizes seizures [62]. Also, the elevated extracellular Glx concentration in those patients can be explained by reduction in glutamate reuptake [31].

ii. Lateralization Epileptogenic Zone

Based on an extensive literature research, the most commonly used ratios for lateralization of the epileptogenic zone are NAA/Cr and NAA/Cho.

Miller et al. [32] reported a study in which asymmetry in NAA/Cr between right and left sides lateralized 92.5% of TLE patients who had lateralization by EEG [45].

Two years later, Azab et al. [37] used the same metabolic ratio to assess the ability of MRS in detecting the lateralization side in patients with TLE in correlation with EEG and MRI findings. According to the EEGs, patients were classified in three groups: unitemporal epileptic focus, bitemporal epileptic focus and normal EEG. When comparing NAA/Cr between the groups, a significant decrease in the patients' groups compared to the controls was found.

Furthermore, out of 40 patients with TLE; EEG detected lateralization in 20 patients (50%) while MRS detected metabolic abnormalities lateralized to one side in 33 patients (82.5%) and MRI detected lateralized abnormalities in 23 patients (57.5%) [37]. It should be noted that MRS could detect metabolic abnormalities in patients with normal MRI, providing an added value and enhancing the sensitivity of MRI.

On top of that, Xu et al. [63] compared the measurements of NAA/Cr and NAA/(Cr+Cho) in the hippocampi of MRI-negative TLE patients and normal subjects. Of the 20 TLE patients, 10 were lateralized to the left side and the other 10 to the right side.

For the NAA/Cr ratios, the ratios ipsilateral to the seizure side were decreased compared with the ratios contralateral to the seizure side (7.28%) and the normal control hippocampi (8.203%). Likewise, for the NAA/(Cr+Cho) ratios, the ratios were decreased in the ipsilateral side compared with the contralateral side and the normal control (6.618 and 8.104%, respectively).

Aun et al. [34] utilized several metabolic ratios, such as NAA/(Cr+Cho), NAA/Cr, and NAA/Cho, to lateralize the epileptogenic focus. Nonetheless, clear concordant lateralization was best achieved with NAA/(Cr+Cho). A reduced ratio allowed lateralization -always to the side with lower value- in most patients in accordance with EEG results.

The NAA/(Cr+Cho) ratio was considered pathognomonic if it was below 0.71 in either unilateral or bilateral cases. On the right temporal lobe, 16 patients were found to have abnormal MRS data and 14, normal, whereas on the left temporal lobe, 15 patients were found to have abnormal MRS data and the other 15, normal.

On comparing MRS with EEG findings: MRS results were nearly consistent with "gold standard" ones in all patients with no significant discrepancy between the two modalities.´

It is worth noting that the use of Asymmetry Index (AI) improved the lateralizing capabilities of the technique especially in bilateral abnormal ratios. 26 patients (about 87% of total patient number) were able to be lateralized with MRS using AI. 16 cases lateralized to the right side (about 53% of total patient number) and 10 cases lateralized to the left side (about 34% of total patient number). The remaining 4 patients (about 13% of total patient number) failed to be lateralized.

Similarly, Hajek et al. [41] made use of the Asymmetry Coefficient (AC), calculated from metabolic concentrations, to lateralize the epileptogenic zone in patients with TLE.

Moreover, Mohamed et al. [35] calculated the Percent Asymmetry Factor (%AF) for lateralization. The majority of the studied patients (25/26; 96.15%) showed significantly increased mean %AF for all estimated peak metabolites concentration ratios: MI/NAA and Glx/NAA.

In another study carried out by Davis et al. [59], MRS corroborated the Glutamate Chemical Exchange Saturation Transfer (GluCEST) findings. GluCEST correctly lateralized the temporal lobe seizure focus on visual and quantitative analysis in all patients with non-lesional TLE based on conventional MRI.

iii. Seizure Spread

The temporal lobe has rich functional interconnectivity with other brain regions, causing the clinical phenomenon of secondary generalization, also known by seizure spread [64].

Vollmar et al. [17] identified widespread extratemporal pathologic MRS signals in TLE patients. NAA/(Cr+Cho) reduction was revealed in the ipsilateral insula, in both frontal lobes, and in the ipsilateral parietal lobe [65]. These findings correlate well with known pathways of seizure propagation from invasive EEG recordings [66].

Miller et al. [32] also reviewed about seizure spread. On the one hand, they reported abnormal NAA both ipsilateral and contralateral to the site of seizure onset, suggesting that the contralateral NAA abnormalities could represent transient neuronal dysfunction related to spread of seizures.

On the other hand, they described MRS abnormalities had been identified in the extratemporal lobe in TLE. Reduction in MI was identified in the frontal lobe of patients with TLE, which may be a temporary effect following recent seizure activity or the cumulative effect of chronic seizures [67]. Moreover, decreased NAA concentration in the frontal, parietal, and occipital lobes both in the ipsilateral and contralateral hemispheres was reported in TLE [68].

The widespread reduction in NAA might be due to the induced excitotoxic process that initially occur in the hippocampus. The loss of efferent neurons in the hippocampus may lead to differentiation and alteration in the function of neurons in other brain regions. Another possible cause might be related to treatment effects from antiepileptic drugs [32].

Over the past few years, the spread of the seizure in the temporal lobe itself has also been studied. Nicolo et al. [54] compiled several studies on reduced NAA ipsilateral to seizure focus [69] [70] [71], including in non-lesional cases [72].

Furthermore, Mohamed et al. [35] proved that areas of seizure spread on the ipsilateral side showed a significant decrease in MI/NAA when compared to their levels on the contralateral side. However, Wellard et al. [73] observed an elevation of MI concentration ipsilateral to the epileptogenic temporal lobe in patients with hippocampal sclerosis compared to the corresponding contralateral temporal lobe and normal controls. They attributed this change to the associated astrocytosis.

Zhang et al. [74] and Davis et al. [59] stated that, in patients with TLE, NAA/(Cr+Cho) value ipsilateral to the epileptogenic focus was not significantly lower than that of the corresponding contralateral regions. Also, Ercan et al. [75] observed a non-significant reduction in both NAA/Cr and NAA/(Cr+Cho) ratios in patients with left TLE compared to normal controls.

However, Simister et al. [60] concluded that TLE was associated with reduction in NAA/Cr ratio in both ipsilateral and contralateral temporal lobes.

These dissimilarities may be referred to differences in the study design, selection criteria, the time of estimation of these metabolites after seizure onset and the disease chronicity [35].

iv. Age Relation

Focusing on the age-related reduction in the concentration of GABA in the TLE group, Gonen et al. [76] also noted the increasing fractional component of CSF with age in patients with TLE as a measure of atrophy, a finding driven by patients with left-sided epileptogenic focus.

Moreover, in TLE patients with hippocampal sclerosis, the ENIGMA study revealed cortical thickness reductions of the bilateral precuneal cortices with left, but not right, seizure focus [77]. This finding goes in line with the results from Gonen et al. Therefore, it is possible that the precuneus region undergoes atrophic changes in patients with left-sided TLE, affecting GABAergic more than glutamatergic neurons.

Table 1. MRS studies in temporal lobe epilepsy

Paper	MRS acquisition	Goal	Metabolite	Change	Notes
Aun et al., 2016	**Single-voxel** (VOI: hippocampus + mesial temporal lobes)	Identification epileptogenic zone	NAA	Decrease	**Cause** – Neuronal loss or damage
			Cr	Increase	**Cause** – Reactive astrocytosis
			Cho	Increase	**Cause** – Reactive astrocytosis
		Lateralization epileptogenic zone	NAA/(Cr+Cho)	Decrease LT: 0.63 ± 0.07 RT: 0.63 ± 0.09	**Info** – Asymmetry Index (AI) improved the lateralizing capacity of the ratio
Azab et al., 2015	**Single-voxel** (VOI: hippocampus + mesial temporal lobes)	Lateralization epileptogenic zone	NAA/Cr	Decrease LT: 1.65 ± 0.50 RT: 1.58 ± 0.46	
Davis et al., 2015	**Single-voxel** (VOI: hippocampus)	Lateralization epileptogenic zone	Glu/Cr	Increase RT: 1.05	
Doelken et al., 2008	**Single-voxel** (VOI: hippocampus)	Identification epileptogenic zone	NAA	Decrease 5.82 ± 0.78	**Info** – NAA cut-off between MRI positive and negative patients
Gonen et al., 2020	**Single-voxel** (VOI: precuneus + posterior cingulate cortex)	Study age relation	GABA	Decrease 1.50 ± 0.20	
Hajek et al., 2008	**Single-voxel + CSI** (VOI: hippocampus)	Identification epileptogenic zone	NAA	Decrease SV: 4.70 CSI: 7.90	
		Lateralization epileptogenic zone	NAA	Decrease SV: 9.90 CSI: 5.30	**Info** – Asymmetry Coefficient
Kuzniecky et al., 2004	**Single-voxel + CSI** (VOI: hippocampus)	Identification epileptogenic zone	NAA	Decrease	
			Cho	Increase	
Miller et al., 2013	**Single-voxel** (VOI: hippocampus + amygdala)	Identification epileptogenic zone	NAA/Cr	Decrease	**Cause** – Reduced NAA due to neuronal cell loss and reactive astrogliosis
			NAA/Cho	Decrease	
			NAA/(Cr+Cho)	Decrease	
			MI	Increase	**Cause** – Induction Na^+/MI cotransporter
		Lateralization epileptogenic zone	NAA/Cr	Decrease	
		Study seizure spread	NAA	Decrease	**Info** – Identified in the frontal, parietal and occipital lobes
			MI	Decrease	**Info** – Identified in the frontal lobe
Mohamed et al., 2020	**CSI**	Identification epileptogenic zone	NAA/Cr	Decrease 0.86 ± 0.11	**Cause** – Reduced NAA due to neuronal loss, seizure duration, frequency and severity or reduction in synaptic density
			NAA/Cho	Decrease 0.94 ± 0.08	
			NAA/(Cr+Cho)	Decrease 0.54 ± 0.62	

			MI/NAA	Increase 1.03 ± 0.21	**Cause** – Elevated MI due to associated astrocytosis
			Glx/NAA	Increase 1.56 ± 1.25	**Cause** – Elevated Glx (within the glial-neuronal unit) due to mitochondrial and metabolic injury and (extracellular) due to reduction in glutamate reuptake
			Glx/Cr	Increase 1.44 ± 0.24	
		Lateralization epileptogenic zone	MI/NAA	Increase LT: 22.00 ± 12.00 RT: 20.50 ± 2.30	**Info** – Percent Asymmetry Factor (%AF) improved the lateralizing capacity of the ratio
			Glx/NAA	Increase LT: 21.50 ± 11.00 RT: 20.00 ± 1.80	
		Study seizure spread	MI/NAA	Decrease 0.50 ± 0.01	**Info** – Identified in the temporal lobe
Nicolo et al., 2019	**Single-voxel** (VOI: hippocampus)	Identification epileptogenic zone	Glx/NAA	Increase	**Cause** – Elevated Glx due to hyperexcitability
			Glx/Cho	Increase	
		Lateralization epileptogenic zone	NAA/Cr	Decrease	
			NAA/(Cr+Cho)	Decrease	
		Study seizure spread	NAA	Decrease	**Info** – Identified in the temporal lobe
Oz et al., 2014	**Single-voxel** (VOI: hippocampus)	Identification epileptogenic zone	NAA	Decrease	
			NAA/Cr	Decrease	
			GABA	Decrease	
Sharma et al., 2020	**Single-voxel + CSI** (VOI: hippocampus)	Identification epileptogenic zone	NAA	Decrease	
			Cr	Increase	
			MI	Increase	
Vollmar et al., 2004	**Single-voxel** (VOI: hippocampus)	Identification epileptogenic zone	NAA/(Cr+Cho)	Decrease	**Cause** – Reduced NAA due to neuronal loss or damage. Elevated Cr and Cho due to gliosis
		Study seizure spread	NAA/(Cr+Cho)	Decrease	**Info** – Identified in the frontal and parietal lobes
Xu et al., 2015	**Single-voxel** (VOI: hippocampus)	Lateralization epileptogenic zone	NAA/Cr	Decrease 1.30 ± 0.13	
			NAA/(Cr+Cho)	Decrease 0.64 ± 0.08	

E. Extratemporal Lobe Epilepsy

There are fewer studies on MRS in ETLE compared to TLE [32]. Nonetheless, table 2 displays the most relevant information from these studies.

Although the temporal lobe is the commonest affected lobe in epilepsy, most patients with ETLE have frontal lobe epilepsy [35].

i. Identification Epileptogenic Zone

Hajek et al. [41] described a significant decrease in NAA/Cho which agreed with the results from the performed EEG, proving a frontal lobe epilepsy with negative or very subtle MR imaging results.

Besides, Miller et al. [32] reported a decrease in NAA in the frontal lobe. However, due to widespread NAA reduction in extratemporal lobe epilepsy, MRS abnormalities may not be adequately localized to identify the seizure focus in extratemporal lobe epilepsy [78].

Most recently, Wang et al. [79] studied neurochemical alterations in the dorsolateral prefrontal cortex (DLPFC) in participants with sleep-related hypermotor epilepsy (SHE) using MRS.

SHE is a focal epilepsy characterized by vigorous hyperkinetic or asymmetric tonic-dystonic seizures occurring mainly during non-rapid eye movement sleep.

Results showed that NAA concentration in the left DLPFC was lower in the SHE group compared with controls. This finding may reflect neuronal energetic impairment of the DLPFC as a chronic consequence of epileptic seizure.

ii. Lateralization Epileptogenic Zone

According to Miller et al. [32], the potential for seizure lateralization is lower in patients with ETLE compared with TLE. Seizure lateralization was achieved in approximately 50% of patients with frontal lobe epilepsy [31] [78].

Along the same lines, Kuzniecky et al. [26] noted, when comparing the coincidence rate between the seizure focus and the reduction of the NAA/Cr ratio, correct lateralization was present in 19 of the 21 TLE patients, but only in 4 of the 7 frontal lobe epilepsy patients.

Table 2. MRS studies in extratemporal lobe epilepsy

Paper	MRS acquisition	Goal	Metabolite	Change	Notes
Hajek et al., 2008	**Single-voxel + CSI** (VOI: hippocampus)	Identification epileptogenic zone	NAA/Cho	Decrease SV: 2.76 CSI: 3.76	**Info** – Identified in the frontal lobe
Kuzniecky et al., 2004	**Single-voxel + CSI** (VOI: hippocampus)	Lateralization epileptogenic zone	NAA/Cr	Decrease	**Info** – Identified in the frontal lobe
Miller et al., 2013	**Single-voxel** (VOI: hippocampus + amygdala)	Identification epileptogenic zone	NAA	Decrease	**Info** – Identified in the frontal lobe
		Lateralization epileptogenic zone	NAA/Cr	Decrease	**Info** – Identified in the frontal lobe
Wang et al., 2021	**Single-voxel** (VOI: dorsolateral prefrontal cortex)	Identification epileptogenic zone	NAA	Decrease 7.19 ± 0.68	**Info** – Identified in the frontal lobe

F. Limitations to the use of MRS

Despite all the progress made so far, the use of MRS in epilepsy still presents certain challenges. To obtain high-quality spectroscopy data, the voxel or ROI must contain sufficient brain tissue and be placed in an area with maximum tissue homogeneity [63].

With improved magnetic field homogeneity and increased magnetic strength, the voxel size can be decreased; however, the greater the magnetic field used, the more extensive the shimming [59].

Also, multislice spectroscopy limits spatial sampling [26] and single voxel acquisition limits spatial resolution, resulting in partial volume effects with contamination of surrounding structures [59].

In addition, due to the limitations of the voxel size and location, some areas which may be affected by TLE or ETLE haven't been investigated in the above-mentioned studies.

Besides, in the majority of the papers, the study population was small and may thus not represent MRI-negative TLE and ETLE in general.

On top of that, comparisons between studies are difficult to make as MRS were acquired from different regions of the brain and therefore ratios can vary significantly depending on their locations. Furthermore, group ages might influence the results as metabolites levels change with growth [32].

IV. CONCLUSION

Epilepsy is one of the most common neurological diseases, thus it is of vital importance to diagnose it. Neuroimaging plays an essential role in identifying the epileptogenic lesions. CT is likely to miss the majority of them and MRI only identifies structural pathology in the epileptic brain in one third of the patients. However, MRS detects abnormalities that are invisible to a conventional MRI because metabolic abnormalities often precede structural changes.

The majority of the reviewed studies confirm that NAA, Cr and Cho are the most commonly used metabolites to identify the epileptogenic zone in MRI negative TLE and ETLE. Moreover, NAA/Cr, NAA/Cho and NAA/(Cr+Cho) are the most widely accepted ratios for lateralization of the normal appearing epileptogenic zone. Furthermore, NAA and MI have been reported as the metabolites that best enable the study of seizure spread.

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