

## Idiopathic generalized epilepsies and efficiency of advanced magnetic resonance imaging techniques in present era; perspectives in future

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### ABSTRACT

Epilepsy is a common disorder worldwide, with a prevalence of 4.5/1000 (0.45%) for youngsters and youths, and 1.54/1000 (0.15%) for the adult Chinese population in Hong Kong. up to 15% of epileptic patients can still leak the screening process of any structural lesion. In addition, the structural lesions detected on structural MR images may not reveal the correct degree and practical position of the abnormalities, especially with respect to malformations of cortical development. These include magnetic resonance spectroscopy (MRS) and perfusion weighted imaging (PWI). The widespread application of most of these techniques in clinical practice depends on the availability of high-performance MR imagers with the ability to accomplish fast echo-planar pulse sequences (echo-planar imaging), as well as substantial data processing capabilities. Using and PWI in study of microcirculation of tissues and vascular of lesional area on mechanisms by which selective drugs work and will provide new treatment targets for drug development. Finally, there is coupling of cerebral blood flow and metabolism, MR perfusion can act as a surrogate marker of metabolism as measured by MRS.

**KEY WORDS:** Idiopathic disease, Epilepsy, magnetic resonance imaging, imaging biomarker, advanced imaging techniques.

### 1. INTRODUCTION

Epilepsy is a common disorder worldwide, with a prevalence of 4.5/1000 (0.45%) for kids and youths, and 1.54/1000 (0.15%) for the adult Chinese population in Hong Kong (Lai, 2010). It has been projected that about 7 to 8% of the population have a minimum, one seizure during their lifetime. Epilepsy is categorized by frequent seizures unprovoked by an acute systemic or neurologic insult (Rasolabadi, 2000). Absences are generalized non-convulsive convulsion. Prior to possible surgical cure, neuro imaging becomes important and mandatory in the work-up of epilepsy localization and the lateralization of seizure foci. The idiopathic generalized epilepsies (IGE) are a group of overlapping epilepsy syndromes (Mullins, 2007). The diagnosis is based on strict clinical and electroencephalogram (EEG) structures as proposed by the International League Against Epilepsy (ILAE). IGE can present at any age, being more common in the first or second decade of life; though, recent studies suggest it presents more often in adults than previously thought (Mullins, 2007). According to the main type of seizure, age of onset of seizures and EEG characteristics, patients may be classified according to the ILAE classification of generalized epilepsies. The International Classification of Epilepsies (1989), acknowledged the heterogeneity of epilepsies with absence seizures, and proposed the categorization of three syndromes of IGE with absence seizures: childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy. Magnetic resonance imaging (MRI) has become the technique of choice and is fundamental for high-resolution structural imaging in epilepsy (Fatehi, 2015). This is due to its ability to achieve superior soft tissue contrast, multi-planar imaging capability, and lack of beam-hardening artifacts, which allows visualization of epileptogenic substrates with greater sensitivity and accuracy. Optimized and dedicated protocols are necessary for assessment of the hippocampus and temporal lobe for atrophy and subtle signal intensity alterations, as well as for detecting certain structural abnormalities such as cortical dysplasia or other developmental abnormalities (Keller and Roberts, 2008). With the development of MR imaging, it has become more subtle with high-field technology, newer hardware, as well as special acquisition and post-processing methods. Yet, up to 15% of patients with epilepsy can still escape detection of any structural lesion. In addition, the structural lesions detected on structural MR images may not reflect the true extent and functional status of the abnormalities, especially with respect to malformations of cortical development. These include magnetic resonance spectroscopy (MRS) and perfusion weighted imaging (PWI) (Parsons, 2002). The widespread application of most of these techniques in clinical practice depends on the availability of high-performance MR imagers capable of performing fast echo-planar pulse sequences (echo-planar imaging), as well as substantial data processing capabilities.

**MRS:** This technique is a noninvasive imaging strategy to providing metabolic information from different body tissues, including the human brain. MRS is a rapidly developing noninvasive technique that allows the clinician to

assess the intact brain for neurochemical changes in a given brain region of interest. In the past 25 years, MRS has been a significant clinically creative diagnostic tool. The detection of these molecules has been valuable in understanding the presence of neuronal elements (NAA), cell proliferation and degradation (choline). Conventional MRI and MRS rely on the same physical principles to collect the MR signal, but differ in the way the data is processed, displayed, and interpreted. Instead of images, as with MRI, data presented as a plot with peak amplitudes compared with a respective frequency is obtained with MRS (Rahmani Tanha, 2016). Various metabolites are detected in the spectrum. Three major peaks characterize long-echo time MRS spectra: N-acetyl aspartate (NAA) - marker of neuronal and axonal viability and density; creatine (Cr) — used as internal reference, since it is the most stable cerebral metabolite; choline- reflecting cellular proliferation. There are two types of MRS techniques: single voxel and multivoxel. Irregularities in many small volume units within the structure, and shows the extension of metabolic abnormalities. Single-voxel MRS is a non-invasive method that portrays the anatomic distribution of metabolite signals, counting those of compounds containing N-acetyl aspartate (NAA), creatine and phosphocreatine (Cr), and choline (Cho). It has consistently demonstrated metabolite changes in the epileptogenic region of the brain. 17 Patients with mesial temporal lobe epilepsy typically reveal extensive reduction in NAA in the temporal lobe and insular cortex, whereas symmetrical generalized reduction of NAA can occur. Therefore NAA asymmetry in the temporal lobe and insular cortex robustly lateralizes the seizure focus. Achten, even postulated an asymmetry index (NAA/Cho+Cr) of more than 0.05 to 0.10 that would point to the diseased side (Lai, 2010). Chernov, also found frequent presence of lactate on the side of epileptogenic zone in addition to decrease in NAA. They continued to postulate a decrease of NAA content below 0.75 and/or unilateral presence of lactate would provide 86% (95% confidence interval, 68-100%) lateralization accuracy. Hence, MRS is a useful adjunctive presurgical test for localizing seizure foci, particularly in temporal lobe epilepsy, and has the potential to reduce the need for intracranial-depth electrode EEG recordings. Multivoxel MRS can achieve higher sensitivity and better spectral quality, improving lateralization of the seizure focus. Magnetic resonance volumetric imaging can sense reductions in volumes of structures functionally connected to the hippocampus, such as the amygdala, entorhinal cortex, fornix, mammillary body and thalamus, and to a far lesser degree, in more remotely connected structures such as striatum and cerebellar hemispheres. Several cross-sectional volumetric studies have revealed a definite relation to the period of epilepsy (Lai, 2010). This was probably due to a combination of neurodevelopmental and progressive effects, characterized by a prominent disruption in the ipsilateral hippocampus and neural connectivity (white matter volume loss) that extended beyond the temporal lobe, and affected both ipsilateral and contralateral hemispheres. It has exposed outstanding sensitivity, ranging from 75 to 92%, and with specificities of 64 to 100% for temporal lobe seizure foci. Thalamic volume loss is typically bilateral, but in the attendance of asymmetry, the smaller side correlates strongly with the onset. The results of MR volumetry in the evaluation of extratemporal epilepsy have been inconsistent so far. Bearing in mind the variation of total cerebral brain volume across different ages, genders, and congenital insults, potential errors can occur (Patariaia, 2007). Several authors have even advocated scaled measurements in relation to total brain volume or direct measurements in a stereotaxic space. Nevertheless, volume measurement generally indicates a later stage of the disease process. A new imaging technique, DTI, makes use of the anisotropic diffusion of water to delineate microstructural tissue organization (Saberri, 2016). Thereby it differentiates pathologic from normal tissue. Data can be displayed in a three-dimensional format referred to as fiber tractography, which allows illustration and visualization of specific tracts such as connections with the language cortex. It has been shown useful in studying cerebral ischemia, acute stroke, multiple sclerosis, schizophrenia, and more recently in epilepsy (Fatehi, 2016). Generally, improved mean diffusivity and reduced fractional anisotropy are observed at the seizure focus. The earlier is more subtle, whilst a left-right diffusivity index/difference can be established to lateralize the epileptogenic focus. Greater lateralization of tracts to the dominant hemisphere was associated with greater decline in naming function, hence the potential to predict language deficits in such patients. By helping to predict visual field defects (superior homonymous quadrantanopia) because of disturbance of the Meyer loop (Bartoli, 2012). Temporal lobe epilepsy has attracted much attention. Past studies reported substantial white matter abnormalities but with limited data on the extent of such abnormalities and their association with clinical factors. Positive correlation of mean fractional anisotropy with delayed memory related to the anterior temporal lobe, and immediate memory impairment linked to the mesial temporal lobe. Lower fractional anisotropy values in the posterior region of corpus callosum were also related to earlier age of seizure onset (Yang, 2002).

Whether the reduction represents an irreversible loss of cells or a potentially reversible metabolic process cannot readily be determined. Nevertheless, our results, by showing metabolite signal changes, detect some pathological processes surpassing the structural changes. Due to technical obstacles, we were unable to statistically analyze the absolute values of respective metabolites (e.g. NAA). Instead, the relative values (ratios) were used (Fojtikova, 2006). Observations and studies using this approach suppose that Cr is a stable internal reference. It is believed that relative signal intensities provide an adequate basis for interpretation of the results and that these intensities are sensitive to neurochemical changes in cell population without regard to absolute metabolite values

(Fojtiková, 2006). However it is assumed that Cr is relatively homogeneously distributed throughout the brain and is not significantly influenced by the epileptic state. In the pathophysiological mechanism of absence seizures, thalamocortical and corticothalamic projections play important roles. The pathophysiology of IGE syndromes is not fully understood, but it is generally accepted that typical absence seizures are the result of abnormal oscillations between the thalamus and cerebral cortex. The neurochemical changes underlying typical absence epilepsy have not yet been fully elucidated, but they are a sphere for active research in both affected humans and in animal models. Epilepsy or an excessive thalamic synchronization, possibly under the control of inhibitory GABAergic mechanisms, remains controversial (Zhao, 2008). It seems that neurons, mostly involved in the thalamic reticular nucleus (nRt), thalamic relay neurons (RNs), and neocortical pyramidal cells comprise a circuit that sustains the thalamocortical oscillatory burst firing of absence seizures. A newly published study, in which authors used MRS, proved a reduction of mean thalamic NAA/Cr in patients with IGE in comparison to normal controls. These MRS results are in line with preceding and current models that the thalamus plays an significant role in the pathophysiology of typical absence epilepsy as has been proven in several subtypes of IGE. To the best of our knowledge, the role of the thalamus in other types of epilepsies (i.e. focal epilepsies) has not yet been clarified. Bernasconi, who studied NAA/Cr ratio in IGE patients, found a negative correlation between thalamic NAA/Cr and the length of epilepsy (Bernasconi, 2003). There was no change in NAA/Cr between the patients whose seizures were well controlled and patients in whom seizures were not controlled. In our current study, there was neither a statistically significant correlation between thalamic NAA/Cr ratio and the duration of epilepsy, nor a correlation with the seizure frequency observed. Due to the small set of values, the absence of correlation may be falsely negative. Our results indicate a downward trend toward the statistical significance in both tested parameters. We can speculate that a statistical significance could be reached with a wider range of values. The generation of bilaterally generalized spike wave discharges is only possible in an anatomically and functionally intact corticothalamic network that is in a suitable state to propagate seizures. The presence of abnormalities in the corticothalamic network has been suggested to be the functional basis of absence seizure generation. Neuronal dysfunction in the thalamus has been indicated by MRS in numerous subtypes of IGE. Other than the metabolic neuronal malfunction, we can also accept a reduction of functional thalamic neurons (reflected by the decrease of NAA), and the possibility of derangement of thalamocortical glutamatergic and intrathalamic GABAergic transmission that might be caused by the mentioned reduction. In general, the metabolite or structural changes may be either a consequence of harm from seizures or a reflection of main underlying pathology as the cause of absence seizures (Fojtikova, 2006). However the significant role of subcortical structures and the pathophysiology of decreased NAA and other metabolite or neurotransmitter disturbances in seizure generation and propagation in IGE has not yet been elucidated (Yang, 2002).

**PWI:** Perfusion MRI can be performed either with the bolus injection of a contrast agent or without any injection. The contrast-agent bolus approach measures the time varying attenuation of T2 or T2\* images caused by the passage of an agent with high magnetic susceptibility through the vasculature (Fatehi, 2016). This method is often referred to as dynamic susceptibility contrast (DSC) MRI. The contrast-free technique uses the spatial selectivity of radiofrequency and gradient pulses to perturb the magnetic properties of water nuclei selectively within the inflowing arterial blood. Because this electromagnetic perturbation effectively labels the endogenous arterial, Water spins, it is known as arterial spin labeling (ASL) (Olivot, 2009).

**DSC-MRI:** All clinically approved MR contrast agents do not cross the normal blood-brain barrier and can be considered intravascular contrast agents in most studies of epilepsy. When a high-susceptibility agent is present in the vasculature, it causes very non-uniform magnetic fields, which lead to attenuation on T2\*- and T2-sensitive MR images. If, as is commonly done, the change in  $1/T_2$  or  $1/T_2^*$  is assumed to be linear in tissue concentration of the agent, then a series of MR images acquired during bolus passage can be converted into concentration versus-time images. Although many clinical uses of DSC MRI use descriptive measures of the bolus passage, such as the time to peak concentration, these dynamic contrast concentration images can be converted into quantitative measures of physiologic variables. Such further quantification of the bolus passage requires removal of the spread of the bolus that results from the intravenous injection and flow through the lungs. Typically, the arterial contrast concentration is inferred from the same images used for perfusion measurement by measuring the signal change in an arterial region of interest. This region can be defined by anatomic criteria, by the early arrival of contrast, by the high blood volume in voxels containing a major vessel, or more typically by a combination of all three. Because the volume of artery in the region is uncertain and the proportionality between concentration and relaxation is likely different in the arterial region than in other tissue, the absolute concentration cannot be inferred from the signal; only the relative concentration as a function of time is determined. The effect of the temporal spread of the arterial input can then be removed by a mathematical process known as deconvolution. The deconvolved tissue curves can then be used to determine physiologic quantities. The peak height of the curve is a measure of perfusion (cerebral blood flow; CBF) relative to other regions in the brain; the area under the curve is a measure of relative blood volume; and the ratio of the two is the absolute mean transit time (MTT). It should be noted, however, that delay and dispersion of the bolus

between the site of measurement of the arterial input function and the region of interest can introduce significant errors in the CBF and MTT measures [e.g, CBF is underestimated by 45% for a delay of 1.5 s]; concentration–time curves must therefore be examined for such characteristics before calculated maps can be regarded as reliable (Fuss, 2001).

**ASL:** Arterial spin labeling (ASL) is another noninvasive technique for quantitative perfusion MR imaging. Relative mesial temporal hypoperfusion demonstrated by continuous ASL perfusion MR imaging correlated well with clinical lateralisation of the seizure side, as well as with 18FDG-PET hypometabolism<sup>49</sup> and hippocampal volume loss. Similar findings were reported using a contrast bolus MR perfusion technique, measuring interictal relative cerebral blood volume in patients with temporal lobe epilepsy (Gharib Salehi, 2016). The continuous ASL technique has the advantage of providing a diffusible tracer and therefore measures classical tissue perfusion. A previous study combining contrast-enhanced MR perfusion and diffusion weighted imaging also provided lateralizing information in non-lesional temporal lobe epilepsy; lower cerebral blood flow and a larger apparent diffusion coefficient in the lesional side. Magnetic resonance perfusion holds promise as a better alternative since it is less expensive, does not involve ionizing radiation, and is more readily available. Yet more and larger clinical trials are needed to validate its use, and determine whether these techniques provide independent data to established MR quantitative measures. Nevertheless, such techniques are expected to continue evolving and provide a means of determining the exact site of origin and propagation pathways for seizures. ASL uses spatially selective radiofrequency and gradient pulses to perturb the nuclear spins of hydrogen in the water molecules of inflowing arterial blood. If time is allowed for the perturbed spins to flow into the tissue being imaged, the perturbation in the inflowing spins will lead to a perfusion-dependent perturbation in the image signal intensity. Because the perturbation decays with T<sub>1</sub>, an MR relaxation time on the order of 1 s, the experiment can be repeated rapidly to obtain high temporal resolution. The greatest disadvantage of ASL is the small signal change it produces (of the order of 1%), which limits its sensitivity. Labeling of arterial blood can be achieved either with pulsed or continuous strategies. In the pulsed strategies, a slab of tissue containing proximal arteries is inverted with a short pulse before imaging. All of the blood is labeled simultaneously, and the effect of the inversion begins to decay with T<sub>1</sub>. Continuous labeling strategies, in contrast, label the blood as it flows past a proximal plane with a technique known as flow driven adiabatic inversion. The continuous-labeling technique is more efficient at labeling the inflowing blood than is the pulsed technique, but it requires more power deposition in the subject and may not be compatible with the radiofrequency amplifiers of some clinical scanners. Absolute quantification of perfusion is arguably easier with ASL than with DSC because one can more accurately control the timing and magnitude of the input function. Because the efficiency and timing can be well estimated, no independent measurement of input function is required. If the labeling is modified to minimize the effects of transit delays and T<sub>1</sub> is measured, quantification of perfusion is possible. It should be noted, however, that such correction (particularly in the case of transit delays) is not simple, and care is required when using data quantitatively (Chao, 2010).

## 2. CONCLUSION

Advancements in the application of MRS in selectively identifying neurotransmitters in neurologic disorders will shed some light on the neurochemical changes associated with disease progression. Also, using and PWI in study of microcirculation of tissues and vascular of lesional area on mechanisms by which selective drugs work and will provide new treatment targets for drug development. Finally, there is coupling of cerebral blood flow and metabolism, MR perfusion can act as a surrogate marker of metabolism as measured by MRS.

**Conflict of Interest:** Authors have no conflict of interests.

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