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Mini-Review

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Differentiation of Brain Abscesses from Necrotic High-grade Gliomas Using Advanced MR Imaging Techniques: A Mini Review

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Abstract

The accurate discrimination between brain abscesses and cystic high-grade gliomas (HGGs) is of great importance for planning adequate treatment and for estimating outcome and future prognosis. MR imaging plays an essential role in the discrimination of these two entities. However, differential diagnosis often becomes difficult as conventional neuroimaging features of brain abscess are nonspecific and may simulate those of cystic rim-enhancing mass lesions of varying etiologies including HGGs. It is well documented that cellular and vascular microenvironment of cystic cavity and enhancing rim of abscess is considerably different from that of necrotic HGG. By exploiting these unique characteristics, several studies have shown the potential of physiologic MR imaging techniques in facilitating better characterization of both of these intracranial cystic lesions. The purpose of this mini review is to summarize the basic principles and clinical role of commonly used advanced MR imaging techniques such as diffusion, perfusion MR imaging and MR spectroscopy in differentiation of brain abscesses from necrotic HGGs. Briefly, we will also discuss the potential role of emerging imaging techniques such as chemical exchange saturation transfer (CEST) in characterizing brain abscesses. We will also describe the existing challenges and limitations of using these techniques in routine clinical settings and will finally discuss possible solutions to avoiding pitfalls in data acquisition, and analysis for future studies.

Keywords

Brain abscesses, Necrotic high-grade gliomas, Advanced MR imaging techniques, Diffusion tensor imaging, Dynamic susceptibility contrast-perfusion weighted imaging, Proton MR spectroscopy, Three-dimensional-echo planar spectroscopic imaging

Introduction

Differentiation of patients with brain abscesses from those with necrotic or cystic high-grade gliomas (HGGs) can present a significant diagnostic challenge. An accurate and timely differential diagnosis is essential as the treatment and prognosis between these two disease conditions are quite different [1]. Brain abscesses are potentially curable and can be treated successfully by means of standard therapeutic interventions or simply by multiple needle aspirations resulting in significantly improved clinical outcomes [2]. However, the morbidity and mortality rates associated with brain abscesses still remain significantly elevated, especially if appropriate treatment is delayed [3]. On the other hand,

necrotic HGGs are managed differently and often require more detailed pre-operative planning prior to surgical resection. However, diagnostic difficulties may lead to a significant delay in adequate planning for these patients. Additionally, incorrect diagnosis of necrotic HGGs carries significant psychosocial ramifications for patients. Unfortunately, conventional MR imaging often yields non-specific findings and fail to definitively distinguish between brain abscesses and HGGs [4]. Therefore, limitations of conventional neuroimaging necessitate the development of alternative imaging biomarkers to discriminate brain abscesses from necrotic HGGs.

The purpose of this review article is to provide an overview of the potential utilities of advanced MR imaging techniques such as diffusion, perfusion MR imaging and MR spectroscopy in distinguishing brain abscesses from HGGs. We will also discuss the existing challenges and limitations of using these techniques in clinical settings and will discuss possible solutions to avoiding pitfalls in study design, data acquisition, and analysis in future studies.

Role of Diffusion MR Imaging

The biophysical mechanism of Diffusion-weighted imaging (DWI) is based on the microscopic random translational motion of water molecules in a biological tissue. The magnitude of translational motion is described by its apparent diffusion coefficient (ADC) values. Brownian motion of water molecules is hindered by various factors such as cellular packing, intracellular organelles, cell membranes and macromolecules present in various tissue compartments. Variation in ADC may reflect changes and redistribution of water molecules between intracellular and extracellular compartments of a tissue [5].

Diffusion-weighted images are typically acquired using strong magnetic field gradients to make the magnetic resonance signal sensitive to the molecular motion of water. Typically, DWI is obtained by measuring the signal loss after the addition of a pair of rectangular diffusion sensitizing gradients (equal in strength and opposite in polarity and effect) to either side of the 180° pulse of a spin-echo (SE) sequence. As a result, of the first pulsed gradient, spins accumulate different phase shifts depending on their positions with respect to the gradient, while application of a second pulsed gradient, or 180° refocusing pulse, causes reversal of the phase shift. For stationary spins, the accumulated phase shift, as a result of the second gradient, will be similar in magnitude but opposite in polarity and therefore, the net phase shift will be zero at the time of echo, and the signal strength will remain intact. However, moving individual spins do not accumulate a similar phase shift during the two gradient pulses. Therefore, at the time of echo, phase shifts will be randomly distributed and will lead to signal attenuation on diffusion-weighted MRI. The degree of signal attenuation, after application of diffusion gradients, depends upon the duration and strength of the magnetic field gradients as well as the measurement of diffusivity and spin–spin relaxation time (T2) of mobile spins.

Several studies [6-8] have shown the potential of DWI by using characteristic signal intensity pattern from centre of a lesion to differentiate between brain abscesses and necrotic HGGs. In general, pus produces a hyperintense signal intensity on DWI and a reduced apparent diffusion coefficient (ADC)/mean diffusivity (MD) value. Conversely, centres of necrotic HGGs present with isointense or hypointense signals on DWI, with increased ADC/MD values. In accordance with these previously published reports, a study from our group [9] also observed a significantly lower MD from the central core of brain abscesses compared to those with necrotic HGGs. Taken together, these findings imply that the central core of infective and necrotic HGG lesions may harbour differential degrees of cellularity, viscosity and cyto-architectural composition (number of inflammatory cells, protein molecules, and arrangement of collagen fibres [8, 10]. In spite of some promising findings, high diffusivity similar to that found in necrotic tumours has been reported in cases of both pyogenic and fungal abscesses that were untreated [11, 12] or treated conservatively [13]. Therefore, ADC/MD ratios should not be considered pathognomonic in the differential diagnosis between abscesses and necrotic HGGs.

In contrast to DWI, diffusion tensor imaging (DTI) allows evaluation of anisotropic water diffusion in three-dimensional space and DTI derived fractional anisotropy (FA) reflects the degree of water anisotropy in tissues [5]. A previous published study [14], has reported high FA from the centre of an actinomycotic brain abscess. Additionally, markedly elevated FA (as high as normally observed from normal white matter) have been reported from the cavities of other pyogenic abscesses [15, 16] and these FA values were significantly higher compared to those of necrotic tumours [17]. It has been postulated that increased FA in abscess cavities is mainly caused by the presence of aggregated neuroinflammatory cells secondary to the release of adhesion molecules by the upregulation of anti-inflammatory processes. When these cell clumps become oriented and organized, they present with an abnormally high FA from the centre of abscesses [18].

A broad data analysis of DTI provides additional parameters such as coefficient of linear (CL) and planar (CP) that describe the shape of a diffusion ellipsoid [5]. These geometric indices have been used to differentiate GBMs from brain metastases and lymphomas [19], to differentiate classic from atypical meningiomas [20], and to characterize epidermoid cysts [21] and brain tuberculomas [22] suggesting that directional organization of tissue microstructures provides additional information, and can therefore assist in further characterizing different tissue types. Using DTI, Toh *et al.* [17] reported significantly higher CL and CP values from the cystic cavities of brain abscesses than from those of necrotic HGGs, supporting the notion of accumulating branching and crossing/kissing pseudofiber structures within the abscess cavity [16, 23]). Congruently, a study conducted by Chawla *et al.* [9] reported significantly higher CP values and a trend towards higher CL values from central cores of brain abscesses than from those of necrotic HGGs. Moreover, findings of significantly greater CP than CL values from central cores of brain abscesses and necrotic HGGS were in agreement with a prior study reported by Kumar *et al.* [16], suggesting the presence of a planar model of diffusion tensor in these lesions. These interesting results also provide a notion that CP values had a greater contribution to the overall increased FA from the

central core of theses lesions than CL values.

Role of Perfusion MR Imaging

Dynamic Susceptibility contrast (DSC) is the most commonly employed perfusion weighted imaging (PWI) method in clinical settings [24]. DSC is an echo-planar imaging sequence based on the T2* signal reduction signal following administration of gadolinium-based contrast agents. From a DSC acquisition, a T2* signal drop curve can be plotted, being proportional to the concentration of the contrast agent. A preload injection of a bolus of contrast agent before the acquisition of dynamic images is known to limit the potential leakage effects in DSC.

The most common quantitative parameter derived from DSC-PWI imaging is the relative cerebral blood volume (rCBV) that is used widely in the clinical settings. It has been reported that, in the absence of recirculation and contrast material leakage, rCBV is proportional to the area under the contrast agent concentration-time curve. In general, the assumptions of negligible recirculation and contrast material leakage are violated in the presence of a neoplasm. The effects of this assumption can be reduced by fitting a gamma-variate function to the measured signal intensity-time curve [25]. Both SE and gradient echo (GRE) based sequences can be used for estimating rCBV. While SE sequence has been shown to be sensitive to small blood vessels, GRE include signals both from large vessels and abnormal vasculature from tumour beds [26]. Rich capillary network secondary to angiogenesis is a common feature of malignant neoplasms responsible for detecting high rCBV from these tumors [27]. A strong correlation between histological grade of gliomas rCBV is generally observed with GRE technique [28].

Using DSC-PWI, significantly higher median rCBV and maximum rCBV (rCBVmax) have been observed from enhancing regions of necrotic HGGs compared to those of brain abscesses [9, 29-32]. The capsule of a brain abscess is primarily composed of relatively mature collagen fibres with a low capillary density [33] and hence, these lesions are generally associated with reduced rCBV, whereas HGGs are characterized by neovascularisation (increased microvascular density) [34], and therefore by high rCBV. Despite significant differences in rCBVmax between the two types of cystic lesions, some cases of fungal abscesses have been known to exhibit rCBVmax greater than the average rCBVmax from all necrotic GBMs [9]. The atypical high rCBV from a Nocardia brain abscess, mimicking an HGG, has also been observed in prior studies [35, 36]. Collectively, these unusual cases emphasize the importance of utilizing a multi-modality imaging protocol for differentiating brain abscesses from necrotic HGGs.

Since, HGGs present with considerable blood-brain barrier breakdown and contrast leakage from intravascular space to extravascular and extracellular compartments, the T2*-weighted signal intensity loss may be concealed by a signal intensity increase secondary to T1 effects. In such cases, underestimation of CBV is generally observed [25] that may mimic CBV values from brain abscesses. In order to reliably compute CBV values, a mathematic leakage-correction model should be used to process the DSC-PWI data.

Role of Combined Use of Diffusion and Perfusion MR Imaging

By combining the distinctive potentials and parameters of DTI and PWI, some studies [19, 37, 38] have shown an elevated diagnostic performance in differentiating between histologic grades of gliomas, subtypes of brain tumours and the true progression from pseudoprogression conditions in patients with glioblastomas. While extending this approach to differentiating brain infections from necrotic GBMs, a study published by Chawla *et al.* [9] obtained a highly accurate discriminatory model in distinguishing brain infections from necrotic GBMs. Given that FA and rCBVmax reflect inherently different biological information, these parameters were complementary and thus interacted synergistically. It is likely that this interaction might have provided greater discriminatory power than what would be expected from individual parameters. The investigator of that study concluded that a combined analysis of DTI and PWI parameters provides greater neurological confidence in discriminating brain abscesses from necrotic HGGs than if these techniques are used in isolation.

Role of MR Spectroscopy

Proton MR Spectroscopy (1H MRS) can non-invasively analyse the metabolic/biochemical composition of normal brain parenchyma as well as of pathological processes [39, 40]. Similar to the basic principles of magnetic resonance imaging (MRI), MRS is based on the spin properties of atomic nuclei (e.g. 1H, 31P, 13C, 19F) when present in a strong magnetic field, that allows the nuclei to absorb and reemit energy in response to a radio frequency pulse at the resonance frequency of that particular nuclei. The effective magnetic field sensed by a particular nucleus is affected by neighbouring electrons. The separation of resonance frequencies of different protons of a molecule due to the dissimilar chemical environment is described as the chemical shift (δ) and is expressed in parts per million (ppm). The height (maximum peak intensity) or the area under the peak yield's relative measurements of the concentration of protons.

The spectral information from a particular region of the brain is generally obtained by spatial localization, which is achieved by applying static and/or pulsed gradients. Localization methods commonly used in clinical 1H MRS include: point-resolved spectroscopy (PRESS), spatially resolved spectroscopy (SPARS), and the stimulated-echo method (STEAM). As abundant water protons (70M) impose limitations to observe intracellular metabolites (1-10 mM), the signal from water needs to be suppressed. The most frequently used method for suppressing the signal from water is chemical shift selective excitation (CHESS), which reduces the water signal by a factor of 1000.

The most prominent resonances that are seen from normal human brain on *in vivo* 1H MRS include N-acetyl aspartate (NAA, 2.02 ppm) together with intense signals from creatine (Cr, 3.03 ppm), choline containing compounds (Cho, 3.22

ppm), myo-inositol (3.56 ppm) and multiple peaks from glutamate and glutamine (Glx, 2.35 ppm).

Several previous studies have the shown potential of 1H MRS in characterizing brain abscesses [41, 42] and differentiating them from necrotic HGGs [30, 43-47]. The distinctive metabolite pattern of brain abscesses includes the resonances of amino acids [leucine, isoleucine, valine (0.9 ppm) and alanine (1.47 ppm)], lactate (1.33 ppm), acetate (1.9 ppm), and succinate (2.4 ppm). The specific spectrum of the abscess cavity is usually significantly different from the spectra of necrotic HGGs that are usually characterized by elevated choline (3.2 ppm) contents along with variable levels of lipid/lactate (1.3 ppm) and diminished N-acetylaspartate (2.02 ppm) levels. Using 1H MRS, Nath *et al.* [43] obtained a sensitivity of 100% and a specificity of 80% in differentiating brain abscesses from necrotic HGGs in a study. Increases in lactate, acetate and succinate presumably originate from the enhanced glycolysis and fermentation of the infecting micro-organisms. Amino acids such as valine and leucine are known to be the end products of proteolysis by enzymes released by neutrophils in pus. Lactate and lipids are non-specific metabolites produced by anaerobic glycolysis and necrotic tissues in brain abscesses. Both lactate and lipid peaks can also be observed in necrotic HGGs and are therefore these metabolites may not be useful markers for differential diagnosis [46]. Although, alanine has been detected in the spectra of meningiomas [48], resonance of alanine is usually not present in necrotic HGGs. More importantly, the appearance of acetate resonance that is considered as a specific marker for *in vivo* detection of pyogenic abscesses may be absent from the spectra of an aerobic bacterial abscess [41].

Multivoxel 1H MRS may be useful in evaluating both cystic cavity and ring-enhancing portions of the lesions. Some investigators [49] have reported normal brain resonances of NAA, Cho and Cr on 1H MRS spectrum from the rim enhancing portion of the brain abscesses. However, investigators of that study envisaged that those metabolites were mainly visible due to the contamination by surrounding brain parenchyma. While analyzing single or multivoxel 1H MRS data from contrast enhancing regions of a cystic lesion, the sampled voxels might include the edges of the necrotic regions or perilesional regions or both. Thus, metabolite levels in such lesions might be influenced by contribution from different tissue compartments. By contrast, the three-dimensional-echo planar spectroscopic imaging (3D-EPSI) method provides metabolite maps with excellent spatial resolution that can be spatially co-registered to anatomical images to facilitate mapping of metabolite alterations from different regions of cystic lesions with less probability of partial volume averaging. Moreover, single voxel or single slice multivoxel 1H MRS may suffer from incomplete sampling of the cystic lesions. The potential of 3D-EPSI in characterizing glioma grades [50], mapping glycine distribution in gliomas, planning radiation therapy for GBM patients [52], identifying residual tumor following radiation therapy (Lin D, 2016) [53], evaluating response to epigenetic modifying agents in recurrent GBM [54], evaluating treatment response to tumor treating fields [55], differentiating true progression from pseudoprogression in glioblastoma patients [56] and in assessing the effect of whole brain radiation therapy on normal brain parenchyma in patients with metastases [57] has been reported. Although 3D-EPSI is a promising spectroscopic tool, the acquisition time of this sequence is a little long (~16 minutes) even after using parallel imaging techniques. Moreover, the value of this sequence in the clinical setting remains unclear, mostly because the number of studies investigating the potential of this technique is small. Larger studies with more statistical power are necessary to confirm the clinical value and the cost-benefit ratio of this relatively new modality.

Role of Chemical Exchange Saturation Transfer (CEST)

Chemical exchange saturation transfer (CEST) imaging relies on a novel contrast mechanism that depends on the exchange between mobile protons in amide (-NH), amine (-NH2) and hydroxyl (-OH) groups and bulk water molecules [58]. Currently, CEST imaging is being widely explored in the study of various neurological disorders in both pre-clinical and clinical settings.

Using a rat brain abscess model in a recent study, Liu *et al.* [59] demonstrated the potential of bacterial CEST (bac-CEST) method in detecting bacterial abscesses and differentiating it from brain tumors. Moreover, bac-CEST contrast was also used to monitor the response of bacteria to antibiotic treatment. Although, the bac-CEST MRI is at an early stage of its development, the promising initial findings are crucial for further optimizing this method and finally enabling the translation into clinical applications.

The metabolite glutamate (Glu) is the most important excitatory neurotransmitter in the central nervous system and plays a vital role in tissue bioenergetics [60]. Our group has developed CEST of Glu (Glu-CEST) method that can be utilized to generate high-resolution parametric maps to better understand the role of this crucial metabolite in studying neurological disorders [61]. It has been demonstrated that Glu exhibits a pH and concentration-dependent CEST effect (Glu-CEST) between its amine group, observed at ~3.0 ppm downfield from bulk water protons. Using a rat model of Staphylococcal brain abscess, Chen *et al.* [62] observed higher Glu-CEST contrast from brain abscess compared to contralateral normal brain parenchyma. Taken together, these studies suggest that CEST is a valuable non-invasive tool for characterizing brain abscesses.

Closing Remarks and Future Perspectives

Despite some clinical limitations and unsolved issues, advanced MR imaging techniques provide quantitative, objective and biologically relevant information in characterizing intracranial cystic mass lesions. The metabolic and physiologic information can help to differentiate brain abscesses from necrotic HGGs. However, it is critical to standardize the imaging protocols for fast-tracking the translation of these techniques into routine clinical applications. Further progress in this field requires data sharing and large multi-centre collaborative validation studies.

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