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Perfusion MR Imaging and Proton MR Spectroscopic Imaging in Differentiating Necrotizing Cerebritis from Glioblastoma Multiforme

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Abstract

We describe a lesion with the MR imaging characteristics of a glioblastoma multiforme and demonstrate how perfusion MR imaging and proton MR spectroscopic imaging can be used to differentiate necrotizing cerebritis from what appeared to be a high-grade glioma. A 43 year old woman presented to her physician complaining of progressive visual disturbance and headache for several weeks. Conventional MR imaging demonstrated a parietal peripherally enhancing mass with central necrosis and moderate to severe surrounding T2 hyperintensity suggesting an infiltrating high-grade glioma. However, advanced imaging, including dynamic susceptibility contrast magnetic resonance imaging (DSC MRI) and magnetic resonance spectroscopic imaging (MRSI), suggested a non-neoplastic lesion. The DSC MRI data demonstrated no hyperperfusion within the lesion and surrounding T2 signal abnormality and the MRSI data showed overall decrease in metabolites in this region, except for lactate. Because of the aggressive appearance to the lesion and the patients worsening symptoms, a biopsy was performed. The pathologic diagnosis was necrotizing cerebritis. After the commencement of steroid therapy, imaging findings and patient symptoms improved. This report will review the utility of advanced imaging for differentiating inflammatory from neoplastic appearing lesions on conventional imaging.

Keywords

Perfusion MR Imaging; Proton MR Spectroscopic Imaging (¹H-MRSI); High Grade Glioma; Cerebritis

1. Introduction

Conventional MRI allows for precise demonstration of intracranial anatomy and characterization of pathology. However, there may be an overlap in imaging findings which may delay or change therapy, particularly in differentiating surgical from non-surgical lesions. Not only will this have a significant impact on morbidity and mortality but unnecessary surgery with deleterious physical, psychological and financial impact to the patient and the health care

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system can be potentially avoided. Advanced MRI techniques, including dynamic susceptibility contrast magnetic resonance imaging (DSC MRI) and magnetic resonance spectroscopic imaging (MRSI), can add in vivo hemodynamic and metabolic information (1-3). Combining conventional and advanced imaging findings is useful in patients where the diagnosis is uncertain.

Therefore, we report a case which demonstrates the utility of both conventional and advanced MRI techniques to solve a diagnostic dilemma. This paper will review the use of DSC MRI and MRSI to distinguish a high grade glioma from necrotizing cerebritis.

2. Case Report

A 43 year old woman presented to her physician with a chief complaint of progressive visual disturbance and headache for several weeks. Neurologic examination was normal. Conventional MRI sequences along with MRSI and DSC MRI were performed on a 1.5T MR scanner (Siemens Symphony, Siemens AG, Erlangen, Germany). The exam was comprised of T1-weighted spin echo (TR/TE=600/14ms) sequence in axial and sagittal planes before and after gadolinium administration, axial turbo FLAIR (TR/TE/TI=9000/110/2500ms), and axial T2-weighted turbo spin-echo (TR/TE=3400/119ms) sequences. Conventional MRI demonstrated a large left parietal peripherally enhancing mass with central necrosis and a moderate to severe degree of surrounding T2 signal abnormality (Figure 1). The T2 signal abnormality involved the splenium and the contralateral parietal lobe, with expansion of the corpus callosum, suggesting an infiltrating glioma. There was a moderate degree of mass effect associated with the mass. No other lesions were identified. Diffusion weighted images (DWI) were also obtained (EPI sequence in axial plane with b-values of 0, 500, and 1000). There was a small area of restricted diffusion (high signal intensity on DWI images, with low signal on the apparent diffusion co-efficient - ADC map) was noted corresponding to the central area of necrosis.

A volume selective 2D MRSI- chemical shift imaging (CSI) sequence (TR/TE=1500/144ms, with outer volume suppression, and interpolated to reduce effective voxel size) was performed. This multivoxel MRSI technique uses a point-resolved spectroscopy (PRESS) double spin-echo sequence for the preselection of the VOI, which was defined to include the abnormality as well as the contralateral normal brain parenchyma. MRSI data demonstrated overall decrease in metabolites, except for elevation of lactate (Figure 2). There was no Choline elevation to suggest a neoplastic lesion.

DSC MRI perfusion technique was also performed. Sixty dynamic susceptibility, contrast-enhanced T2*-weighted gradient-echo echo-planar images were acquired during the first pass of a single dose (0.1mmol/kg) bolus of gadopentetate dimeglumine (1). Ten axial sections were selected for perfusion imaging through the lesion based on T2-weighted and FLAIR images. Data processing was performed by using a Unix workstation with analytic programs, developed in-house using the C and IDL programming languages. Multiple rCBV (relative cerebral blood volume-relative to contralateral normal brain), CBF (cerebral blood flow), and MTT (mean transit time) measurements were made in the lesion and the normal parenchyma, using multiple regions of interest that were placed at the color overlay maps visually co-registered with the axial post-contrast T1-weighted images to include the areas of maximal enhancement. DSC MRI data demonstrated hypoperfusion within the lesion or surrounding T2 signal abnormality (Figure 3). The rCBV in 4 ROIs placed on the rCBV color overlay map were 0.85, 1.11, 0.31, and 1.1, relative to contralateral normal appearing white matter.

The patient underwent stereotactic biopsy to exclude neoplasia, as the lesion still appeared suspicious on conventional imaging. The biopsy demonstrated necrotic brain parenchyma with an inflammatory infiltrate within the vessel (Figure 4). There is evidence of fibrinoid necrosis

within the vessel wall (involving the intima, media and adventitia- pan vasculitis) in keeping with an inflammatory vasculitic process. There is also evidence of vascular necrosis leading to vascular occlusion accounting for the reduced perfusion on imaging. Azocarmine stains demonstrated connective tissue confirming the pathology to be within vessel wall where again, there was a dense inflammatory cellular infiltrate of the vessel wall with resultant fibrinoid necrosis. The cellular infiltrate is composed mainly of lymphocytes and histiocytes. The final histopathological diagnosis was necrotizing cerebritis. The patient was commenced on steroid therapy which resulted in an improvement in the imaging findings and symptoms.

3. Discussion

Differentiating high grade glial tumors from non-neoplastic lesions, such as infarcts, tumefactive demyelinating lesions and cerebritis can often be sometimes difficult on conventional MR imaging (4,5). All of these lesions may demonstrate variable contrast enhancement, central necrosis, surrounding edema/infiltration and mass effect. Correct differentiation of these lesions is imperative, for they each require different treatment. The consequences of incorrect therapy may be devastating. Advanced MRI techniques, including DSC MRI and MRSI, can add in vivo hemodynamic and metabolic information, and therefore increase diagnostic specificity.

Contrast enhancement is due to breakdown of the blood-brain barrier. Therefore contrast enhancement is variable, seen more commonly in high grade tumors as compared to low grade tumors (6). In addition, contrast enhancement can be seen in many non-glial and non-neoplastic lesions. Central necrosis can also be seen to different degrees in many neoplastic and non-neoplastic lesions, usually occurring when the lesion outgrows its blood supply, and therefore limiting its usefulness as a differentiating characteristic. The degree of surrounding edema and mass effect may help characterize the aggressiveness of a lesion and may be the cause of the patients symptoms. However, this does not help in further characterizing the lesion into neoplastic versus non-neoplastic, glial versus nonglial.

Growth and malignant transformation of brain tumors primarily relies on vascular proliferation. DSC MRI perfusion imaging, though the determination of rCBV (relative cerebral blood volume), CBF (cerebral blood flow), MTT (mean transit time), TTP (time to peak), provides an in vivo assessment of tumoral vascularity and angiogenesis. Gliomas, particularly high grade gliomas, will demonstrate elevated rCBV and CBF with decreased MTT. Evaluation of the peritumoral rCBV can be used to help differentiate a primary glial tumor from a metastasis (7). Glial tumors are infiltrative neoplasms and there are tumor cells in the surrounding T2 signal hyperintensity which will demonstrate elevated rCBV (Figure 5), whereas metastases are non-infiltrative, and the surrounding T2 signal hyperintensity is edema, showing a non-elevated rCBV. Cerebritis will demonstrate reduced rCBV, CBF and a prolonged MTT. There should also not be evidence of increased rCBV in the peritumoral edema as shown in figure 3.

MRSI is a useful means of studying the biochemistry of a lesion relative to normal brain by the estimation of cell metabolites. The basic metabolites involved in evaluation of brain tumors is Choline (Cho), Creatine (Cr) and N-Acetyl Aspartate (NAA). The increase in Cho indicates cell membrane turnover, proliferation and altered Cho metabolism (3). NAA is a marker of neuronal density and viability. Decrease in the NAA metabolite represents replacement of normal functioning neuronal tissue with neoplastic tissue. Cr is a marker of “energy metabolism”, decreased in tumors due to the increased metabolic activity. Two dimensional MR spectroscopy techniques interrogate an area within a single slice of brain, providing a large dataset of measurements throughout lesions and within the adjacent or contralateral normal appearing brain tissue. MRSI usually demonstrates a markedly elevated Cho with respect to Cr and NAA within the tumor and peritumoral area indicating a high grade glioma with tumor

infiltration into the surrounding tissues (Figure 5). On the other hand, an inflammatory process such as a necrotizing cerebritis will demonstrate an overall decrease in metabolites. We also observed a Lactate (Lac) peak at 1.3 ppm. Lac is a product of anaerobic metabolism and is commonly seen in ischemic brain, inflammatory lesions and some infections such as bacterial abscesses and parasitic cysts.

Vasculitis is a spectrum of disorders characterized by varying degrees of blood vessel wall inflammation. No generally accepted classification scheme is agreed upon, however the etiologies can be divided either into infectious/non-infectious or can be divided based on the pathophysiologic mechanism (8,9). A full discussion of all of the etiologies of vasculitis is beyond the scope of this article. Noninfectious vasculitides are characterized by inflammatory cell infiltrate, with varying degree of multinucleated giant cells, granuloma formation and fibrinoid necrosis (10). Several of these vasculitides result in vessel wall fibrosis if the disease state becomes chronic. There is variation within the vasculitides in terms of involvement of what part of the vessel wall (intima, media, adventitia) and within what type of vessel (large-vessel, medium-vessel, small-vessel, or vein) is involved. The systemic vasculitides can cause neurologic symptoms by either primarily affecting cranial vessels or secondarily by causing vascular occlusion or embolism.

Primary angiitis of the central nervous system (PACNS), also termed granulomatous angiitis of the central nervous system, is the only vasculitis that the central nervous system is the main target organ (8). PACNS is composed of a heterogeneous group of histologic states, affecting the vessels to different degrees resulting in a variety of clinical symptomatology and clinical outcomes (11). It predominantly involves small and medium sized cortical, subcortical, and leptomeningeal arteries. It primarily affects the vessel wall intima and media, but may affect the entire wall causing a pan-vasculitis (10).

Headache is the most common presenting symptom, in addition to changes in mentation and level of consciousness. A wide range of imaging findings have been documented, including stroke, hemorrhage, diffuse white matter abnormalities, mass lesion or evidence of meningitis (11). Angiography has been used as a diagnostic and confirmatory tool. Although highly sensitive for vasculitis, angiography is also fairly nonspecific. Angiography demonstrates segmental areas of narrowing and dilation, vascular occlusion, indistinct vessel margins and collateral formation (11). CSF analysis should be obtained to evaluate for elevated protein and lymphocytic pleocytosis. Biopsy is obtained to confirm the diagnosis of vasculitis and differentiate within the vasculitides. The biopsy should focus on an area of contrast enhancement. If there are no enhancing areas noted on MRI, a wedge biopsy of the subcortical region, cortex and leptomeninges from the anterior tip of the non-dominant temporal lobe should be obtained.

With conventional MRI imaging, the radiologist can only surmise the diagnosis in this case based on the imaging characteristics of the lesion, including the enhancement and its surrounding edema and mass effect. This leaves the clinician in a diagnostic dilemma. Both DSC MRI perfusion imaging and MRSI help to further narrow down the differential diagnosis. Perfusion imaging can show that the lesion itself and the surrounding T2 hyperintensity do not show an elevated rCBV, therefore this lesion is unlikely to be neoplastic. MRSI confirms this by not demonstrating any elevation in Cho, but rather an overall decrease in metabolites.

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Figure 1.

A 43 year old woman who presented to her physician with a progressive visual disturbance and headache for several weeks. **A.** Post contrast CT and conventional MRI **B.** FLAIR, **C.** T2-weighted, and **D.** Post gadolinium T1-weighted images, in the transverse plane, demonstrating increased T2 signal intensity within the left temporoparietal region extending into splenium of the corpus callosum (arrow), with associated mass effect and effacement of the left lateral ventricle. There is peripheral enhancement with central areas of what appears to be necrosis. **E.** DWI and **F.** ADC map demonstrates a ring of high signal on diffusion with a corresponding ring of low signal on the ADC map. The conventional MR and the DWI findings proved to be a diagnostic dilemma, with the most likely differential diagnoses of glioblastoma multiforme, lymphoma or a necrotizing cerebritis.

Figure 2.

A. MRSI (TE 144 ms) spectral map demonstrates normal appearing spectra within the contralateral normal brain. Note that the metabolites within the abnormal brain are all reduced with no elevation in Cho. **B.** MRSI (TE 144ms) showing a spectrum from a voxel placed at the normal right hemisphere. The spectrum from voxel [1] demonstrates normal Cho levels [Cho (n)], which is used as a control for comparing the abnormal side. **C.** MRSI (TE 144ms) showing a spectrum from the lesion [2] demonstrating a general decrease in Cho, NAA and Cr. **D.** MRSI (TE=144ms) spectrum from a voxel in the lesion [3], demonstrates minimal NAA and Cho with a large lactate peak (doublet at 1.33pm inverted below the baseline). The marked reduction in all metabolites, particularly in Cho / Cho_n is in keeping with inflammatory/non-neoplastic disease, the final diagnosis being necrotizing encephalitis. A glioblastoma multiforme or CNS lymphoma would have demonstrated marked elevation in Cho / Cho_n

Figure 3.

A. Gradient echo axial DSC MRI with rCBV color overlay map, and **B.** Gradient echo axial DSC MRI with rCBV color overlay map demonstrating the location of five regions of interests (ROIs) placed within [1] normal appearing contralateral brain [2] the anterior portion of the lesion [3] the lateral portion of the lesion [4] the darker necrotic portion of the lesion and finally [5] the posterior portion of the lesion within the edema. The rCBV in these 4 ROIs relative to the contralateral normal brain were 0.85, 1.11, 0.31, and 1.1 respectively. **C.** Signal intensity versus time curves numbered according to the 5 ROIs placed on the rCBV map demonstrates the rCBV to be approximately the same as the contralateral normal brain with reduced rCBV within the edge of the necrotic region ROI [4]. The combination of decreased or normal rCBV and decreased metabolites on MRSI in the lesion and the perilesional regions was highly suggestive of a non-neoplastic diagnosis. The final diagnosis was necrotizing encephalitis.

Figure 4.

A. Hematoxylin and eosin (H & E) stains ($\times 20$) demonstrating necrotic brain parenchyma with a necrotic vessel (arrow). **B.** Higher power ($\times 100$) demonstrates an inflammatory infiltrate within the vessel. There is evidence of fibrinoid necrosis within the vessel wall in keeping with an inflammatory vasculitic process. **C.** H & E ($\times 20$) again demonstrating a dense inflammatory cellular infiltrate of the vessel wall. **D.** Higher power ($\times 100$) again confirming numerous inflammatory cells causing vascular necrosis and vascular occlusion (arrow) accounting for the reduced perfusion on imaging. **E.** Higher power ($\times 100$) demonstrates fibrinoid necrosis of the vessel wall again with vascular narrowing. **F.** Azocarmine stain ($\times 200$) demonstrating connective tissue (stained blue, white arrow) within the vessel wall. **G.** Higher power ($\times 200$) demonstrates necrosis of the intima, media and adventitia in keeping with a pan-vasculitis resulting in vascular narrowing. **H.** Azocarmine stain ($\times 200$) demonstrating connective tissue (stained blue, white arrow) within the vessel wall. There is again a dense inflammatory cellular infiltrate of all layers of the vessel wall (black arrow) with resultant fibrinoid necrosis.

Figure 5.

A 70-year-old woman with a histologically confirmed high-grade glioma. **A.** Axial T1-weighted image post-gadolinium shows a lesion in the right thalamic region with heterogeneous peripheral contrast enhancement with a central cystic/necrotic region. **B.** Axial FLAIR image shows increase in T2 signal within the lesion with moderate surrounding edema. The patient also has hydrocephalus and transependymal edema around the ventricles. **C.** Gradient-echo axial DSC MRI with rCBV color overlay map, shows a high rCBV of 3.70 in keeping with a high-grade glioma. **D.** Cho color overlay metabolite map showing the region of increased Cho. **E.** Spectral map shows regions of Cho elevation within the region of abnormal signal as well as tumor infiltration beyond the region of enhancement, particularly anteriorly and potentially across the midline into the left thalamus. **F.** Spectrum (TE 144 ms) from the peritumoral region showing marked Cho elevation with respect to Cr and NAA indicating tumor infiltration as compared with a lack of Cho elevation in necrotizing cerebritis.