Advanced MR techniques in differentiation and characterization of intraaxial brain lesions

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Learning objectives

In an educational manner discuss the use of advanced MRI techniques, such as MR spectroscopy (MRS), diffusion- (DWI) and perfusion weighted imaging (PWI). Typical cases with accompanying images is presented to clearly depict advantages, disadvantages and technical pitfalls.
Background

Magnetic resonance spectroscopy

MRS is a technique which is able to depict in vivo metabolic information in a specified volume. The important metabolites in brain tumor diagnosis are choline (cho) which is a membrane marker and show cellular turnover. Thus, cho usually is raised in most brain tumors. Creatine (Cr) is an energy marker and in most conditions a stable marker. The choline creatine ratio (cho/cr) is often markedly raised in tumors unless the volume examined is not placed in a necrotic area. The third important metabolite is \( N \)-acetyl aspartate (NAA), which is considered a neuronal marker but its function is not clearly revealed. In tumor diagnosis, NAA is often decreased due to neuronal damage and hence the cho/NAA ratio is an important parameter in tumor diagnosis. Lactate (lac) is a marker of non-oxidative glycolysis and is normally not present in a normal brain parenchyma. Lactate is sometimes difficult to distinguish from overlapping lipid resonances. The use of an echo time (TE) of around 140 ms leads to an inversion of the lactate peak, differentiating it from lipids. Lipids are sometimes originating from the brain itself but may be a result of contamination from lipids in the scalp. Thus, careful planning is required (1).

High grade glioma vs solitary metastasis

Conventional contrast-enhanced magnetic resonance imaging (MRI) has a limited capacity to differentiate a solitary metastasis from high grade gliomas, because of their similar neuroimaging appearance (2, 3). Brain metastases can sometimes be diagnosed on the basis of known primary cancer (especially emanating from lung, breast, kidney, intestine or melanoma) or multifocal presentation in conventional neuroradiology. Differentiation between primary brain tumor and metastasis is crucial for the decision of treatment regime. Histological confirmation is often obligate prior to treatment but there are significant risks associated with the biopsy procedure (4). MRS has proven to help in differentiation between primary and metastatic brain tumors (2, 3).

Grading of gliomas

Gliomas are the most common primary neoplasm of the central nervous system (5). Grading of gliomas is clinically crucial because treatment of high grade gliomas (WHO grade III-IV) significantly differs from that of low grade gliomas (WHO grade I-II) (6). Histopathologic assessment is the current criterion standard for tumor grading but is afflicted with some limitations as mentioned above. Glioma grading based on conventional contrast-enhanced MRI is sometimes unreliable with the sensitivity of glioma grading ranging from 55.1-83.3 % (7). Dean et al. (8) determined that the two
most important predictors of tumor grading using conventional contrast-enhanced MRI were mass effect and necrosis. The amount of contrast enhancement and the presence of peritumoral edema as a predictor of tumor grading are rather elusive. The peritumoral hyperintensity shown on T2 weighted imaging is non specific and represent vasogenic edema, tumor infiltration or a combination of both. Thus, conventional contrast-enhanced MRI is not able to provide information about cellularity, angiogenesis, microvascularity, micronecrosis and metabolism which are important factors in the procedure of grading gliomas (7).

Perfusion weighted MRI (PWI) is a method that includes measurement of relative cerebral blood volume (rCBV). More recent studies have shown that there are statistical significant correlations between increased rCBV in the non necrotic tumoral area and glial tumor grade (9-11). Tumor aggressiveness and growth are associated with endothelial neovascularization and hyperplasia (12), which expressed as an increased rCBV.

Diffusion weighted imaging (DWI) is another aspect of advanced MRI technique that reflects the rate of microscopic water diffusion. There is evidence that lower apparent diffusion coefficient (ADC) is associated with higher cellular density, hence higher tumor grade (13-16). However another study has presented conflicting results (17). The diagnostic accuracy may be elevated if one assesses both the ADC value and rCBV in combination (7).

Primary central nervous system lymphoma

The correct differentiation of primary central nervous system lymphoma (PCNSL) and glioblastoma multiforme (GBM) is important because of differences in both prognosis and treatment. Ultimately the final diagnosis is often revealed by histopathological evaluation. Studies have shown that neovascularization is not associated with PCNSL, leading to a lower rCBV in the tumoral area compared to GBM. rCBV is often even lower in PCNSL than in anaplastic astrocytomias and metastases (18). The knowledge of PCNSL's high sensitivity to steroids is important. Steroids lower both vasogenic edema and rCBV due to changes in blood tumor barrier (BTB) and may lead to misinterpretation. (19). MRS has in a typical case a quite determined appearance with a very high cho peak, near absent cr and the presence of lipid peak (1, 20). Again the combination of rCBV and MRS may raise the diagnostic accuracy.

Post radiation injury vs tumor recurrence

Radiosurgery is used to treat several tumors including malignant gliomas and metastatic brain tumors as an alternative to surgical resection (21). Conventional contrast-enhanced MRI is not able to distinguish post radiation injury from recurrent tumor because of
morphological similarities (21, 22). MRS as well as perfusion weighted MRI have proven to be a fairly robust tool in this distinction. Elevated cho/cr, cho/NAA and decrease in NAA/cr suggested recurrent tumor compared to radiation injury/radiation necrosis with a sensitivity of 85 % and specificity of 69.2 % (22). rCBV calculated from perfusion-weighted MR imaging reflects, as mentioned above, neovascularization and endothelial hyperplasia. A decrease in rCBV values compared to the pre-radiation image indicates tumor response regardless of increase in tumor volume. Higher rCBV values in enhancing component of the mass after radiosurgery may be indicative of tumor recurrence (21).
Fig. 1: A 67-year-old man with glioblastoma multiforme (GBM). A: Axial post-contrast T1WI. B: MR spectroscopy color map. C: MR spectrum, showing a tumor with strong enhancement (arrow, A) with central necrosis. The color map shows the maximum cho/cr ratio in the inner portion of the tumor (arrow, B). Metabolite spectrum shows a very high cho peak (arrow, C) with a cho/NAA ratio of 23 and a cho/cr ratio of 4.3, typical of a malignant glial tumor. These ratios were also high in the edema anterior to the tumor, which helped to differentiate GBM from solitary metastasis.

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Fig. 2: (A-B) 71-year-old man with CNS lymphoma: (A) Axial post-contrast T1WI, and (B) CBV map of perfusion-weighted images showing homogeneous contrast enhancement (arrow, A), and low CBV (arrow, B). (C-D) 65-year-old man with glioblastoma multiforme: (C) T2WI, and (D) CBV map of perfusion-weighted images showing high signal intensity on T2WI and high CBV on PWI (arrows).

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Imaging findings OR Procedure details

Imaging findings in different intra-axial brain tumors

In the contrast-enhanced morphological MRI it is often difficult to differentiate between solitary metastases and GBM. Multiple lesions and known primary malignancy increases the likelihood of metastatic disease. In MRS, primarily the choline creatine ratios (cho/cr) measured in the tumoral core, peritumoral edema and in normal appearing white matter in the contralateral hemisphere are obtained and scrutinized. GBM is an infiltrative tumor where pathological spectra, especially cho/cr ratio are high in the peritumoral area. Metastasis is a delimited process and thus show almost normal or a lower ratio of cho/cr in the peritumoral area. In PWI, typically GBM has an elevated rCBV in the non necrotic tumoral and peritumoral area due to neovascularization and endothelial hyperplasia. These two methods in combination gives important clues to final diagnose (2, 3).

The rCBV in the peritumoral area in gliomas is of help to assess the tumoral grade. High rCBV ratio is suggestive of higher tumor grade. Compared to MRS with calculated metabolite ratios, rCBV measurement has superiority. If one combines both rCBV values and MRS metabolite ratios the sensitivity and specificity for determining a high grade glioma was in one study 93.3 % and 60 % respectively (6).

Studies have shown correlation between high grade gliomas and restricted molecular movement (diffusion), thus a low ADC value, which means low molecular diffusion, is a marker for higher tumor grade (7).

The hallmark of PCNSL in MRS is a very high peak of cho and low or absent peak of cr combined with visible lipid complex. However, PWI is the modality that showed to help differentiating PCNSL from high grade gliomas. In PWI, PCNSL has a very low rCBV. Unfortunately, the findings mentioned above are not always present which leads to invasive biopsy in most cases (20, 23)

Procedure details

The images shown are obtained in a 3T Siemens Magnetom Trio at Skåne University Hospital, Malmö, Sweden.

Perfusion imaging was performed by injecting gadoterate meglumine (Dotarem ®) 0,1 mmol/ kg b.w. at an injection rate of 5 ml/s followed by 20 ml saline flush.

Both perfusion and spectroscopic data were processed by using Siemens Leonardo post processing workstation.
MRS were obtained with chemical shift imaging (CSI) at TE 135 ms

**Imaging parameters were:**

**Axial T2 TSE:**
- TE 109 ms
- TR 4090 ms
- NSA 3
- FOV 230 mm
- Thickness 4 mm
- Matrix 199 x 256

**Axial T1 SE:**
- TE 8.5 ms
- TR 500 ms
- NSA 2
- FOV 230 mm
- Thickness 4 mm
- Matrix 190 x 256

**Diffusion weighted EPI:**
- TE 91 ms
- TR 3500 ms
- NSA 4
- FOV 230 mm
- Thickness 5 mm
- Matrix 143 x 192
Perfusion weighted EPI:

TE 32 ms
TR 1400 ms
NSA 1
FOV 230 mm
Thickness 5 mm
Matrix 128 x 128
Fig. 3: A: Axial T2 weighted image in a patient with histopathologically verified GBM, showing moderate edema and mass effect. B: Axial post contrast T1 weighted image showing inhomogeneous contrast enhancement. C: Axial calculated ADC image showing predominantly low ADC-value representing high cellular density and low molecular movement, indicating high grade tumor (arrow). D: Perfusion weighted MRI showing high rCBV in the non-necrotic part of the tumor (arrow).

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Fig. 4: Same patient as above. CSI MRS TE 135 shows high cho/cr, high cho/NAA and low NAA/cr consistent with high grade glioma.

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Fig. 5: Young man with low-grade astrocytoma: Axial T1WI (A), axial T2WI (B), rCBV map (C), and MR spectroscopy (D) of a patient with a large tumor in the right frontal lobe (arrows A-B). PWI shows low rCBV (arrow C) and MR spectroscopy shows a high cho peak (arrow D), with a cho/cr ratio of 1.5. Despite a very high cho/NAA ratio of 14.3, the radiological diagnosis was low-grade astrocytoma, which was also the histopathological diagnosis obtained at biopsy.

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Fig. 6: A: Axial T2-weighted image in a patient with histopathologically verified brain metastases from breast cancer. Two cystic lesions are visible. B: T1 contrast-enhanced image shows ring enhancing pattern with subtle enhancement in the solid part (arrow). C: The rCBV value is not raised in the peritumoral area which supports the metastasis diagnosis. D: CSI SE TE135 MRS shows normal ratios between cho, cr and NAA in the peritumoral area. Although, there are some lactate indicating hypoxia and/or ischemia. MRS supports the metastasis diagnosis.

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Fig. 7: A: T2W-axial image of a patient with lung cancer and histopathologically verified metastasis. The image shows a lesion with cystic appearance and relative little peritumoral edema and slight mass effect. B: Axial contrast-enhanced T1W-image shows a cystic lesion with ring enhancement and enhancement of the solid part (arrow). C: The MR perfusion study shows low rCBV in the peritumoral area supporting the metastasis diagnosis. D: CSI SE TE135 MRS, localized adjacent to the solid contrast enhancing tumor portion shows almost normal levels of cho, cr and NAA supporting the metastasis diagnosis. Similarly, as in figure 6, there are some lactate.

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**Fig. 8:** A: Axial T2W image in a patient with a histopathologically verified lymphoma. It shows slight mass effect and difficulty to distinguish the lesion from the surrounding edema. B: Contrast-enhanced axial T1 weighted image differentiates between lesion and edema. There is homogeneous contrast enhancement. C: ADC image shows low ADC-value in the contrast-enhancing tumor whereas the surrounding vasogenic edema shows high ADC-value. D: Perfusion weighted MRI shows slight increased rCBV (arrow) only in the medial part of the tumor, which might reflect some angiogenesis in this part of the tumor. The remaining part shows no increase in the rCBV, which is the usual finding in lymphomas.

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**Fig. 9:** Same patient as above. CSI SE TE135 MRS shows a very high cho and a very low cr peak, given a cho/cr ratio of 12. This is not specific but supports the lymphoma diagnosis.

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Conclusion

The use of DWI, PWI and MRS in the diagnostic routine of intra-axial brain tumors markedly improves the accuracy of differentiation between primary and metastatic lesions, in grading gliomas, and in differentiating between high grade gliomas and lymphomas. Furthermore, these modalities might help to distinguish tumor progression and the early response to radiation and chemotherapy (true progression versus pseudoprogression) as well a tumor recurrence and delayed radiation injury. This may reduce the need for invasive procedures to obtain histopathologic biopsies and speed up the process for an earlier and correct treatment that affects quality of life and survival rate.
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