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High-dose gadolinium-enhanced MRI for diagnosis of meningeal metastases

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Abstract We compared high-dose (0.3 mmol/kg) and standard-dose (0.1 mmol/kg) gadolinium-enhanced MRI for diagnosis of meningeal metastases in 12 patients with suspected meningeal metastases. They were imaged with both standard-dose and high-dose gadolinium. All patients with abnormal meningeal enhancement underwent at least one lumbar puncture for cerebrospinal fluid (CSF) cytology, while patients with normal meningeal enhancement were followed clinically. All patients with negative CSF cytology also were followed clinically. A single observer reviewed all the images, with specific attention to the enhancement pattern of the meninges. Abnormal leptomeningeal enhancement was present in three cases, and abnormal pachymeningeal enhancement in three other patients. All of these patients had abnormal CSF analyses. In two of the three cases of abnormal leptomeningeal enhancement the disease was more evident on high-dose than on standard-dose imaging; in one case the abnormal enhancement was visible only on high-dose imaging. In one of the three cases with abnormal pachymeningeal enhancement, the disease was evident prospectively only with high-dose imaging.

Key words Leptomeninges metastases · Magnetic resonance imaging

Introduction

The frequency of meningeal metastases in cancer patients is increasing. Unfortunately, the diagnosis often is problematic, as multiple lumbar punctures for cerebrospinal fluid (CSF) cytology may fail to detect leptomeningeal spread in up to 15–20 % of cases [1]. Currently no imaging modality reliably detects leptomeningeal metastases; even standard-dose gadolinium-enhanced MRI may fail to detect the disease in some cases [2–5]. Furthermore, the sensitivity of imaging tests for leptomeningeal disease has been overstated, because the standard for disease detection, CSF cytology, sometimes fails to detect the disease.

The presence of leptomeningeal metastases alters not only prognosis but also therapeutic options, since intrathecal chemotherapy is required to treat these foci of disease. Thus, the development of imaging protocols more sensitive than those currently available is desirable. We report our experience with high-dose gadoteridol MRI in the diagnosis of meningeal disease.

Patients and methods

All patients involved in this study gave informed consent and were studied in compliance with a protocol previously approved by our institution's Human Subjects Research Committee.

All patients underwent both standard-dose (0.1 mmol/kg) and high-dose (0.3 mmol/kg) examinations within 5 days of each other (1–5 days, mean 1.6 days). All studies were performed on a 1.5-T imager. T1-weighted (TR/TE 500/15) axial and coronal images before and immediately after injection and precontrast axial proton density-weighted (TR/TE 2000/20) and T2-weighted (TR/TE 2000/80) images were obtained in all patients. Prospective in-

terpretation of the images was performed by an experienced neuroradiologist (L. G.), blinded to the dose used in the examinations.

We studied 12 patients, 11 with a known primary tumor (breast carcinoma 4, lung carcinoma 2, melanoma 2, lymphoma 3) and one patient without a known primary tumor. All patients with abnormal leptomeningeal or dural contrast enhancement underwent at least one lumbar puncture. Patients without abnormal contrast enhancement were followed clinically.

Results

Abnormal high-dose images were seen in seven of 12 patients. Leptomeningeal disease was seen on high-dose imaging in three patients, in one of whom the enhancement pattern was considered normal on standard-dose images, although the reader was suspicious of abnormal enhancement in the right temporal lobe (Fig. 1). In this patient, the high-dose images demonstrated obvious, nodular leptomeningeal enhancement in this region. In addition, however, the high-dose images revealed widespread abnormal leptomeningeal enhancement along the medial right temporal lobe and within the left Sylvian fissure. These latter regions had been thought completely normal on the standard-dose images (Fig. 1). In another of the three patients enhancement was notably more evident with the high dose (Fig. 2), as evidenced by increase in both extent and nodularity. The third patient had abnormal leptomeningeal and pachymeningeal enhancement, both seen slightly better on the high-dose images (Fig. 3).

Isolated abnormal pachymeningeal enhancement was seen in three patients. It was equivalent on standard- and high-dose images in two patients, one of whom had CSF cytology positive for metastatic breast carcinoma and one positive serology for Lyme disease and an elevated CSF protein. The third patient had a standard-dose study initially interpreted as normal. The high-dose images clearly demonstrated the abnormal duramater, and, after comparison with these images, the standard-dose images were also seen to be abnormal. This patient had been treated with cranial irradiation and steroids for documented leptomeningeal lymphoma 1 month before entering our study. Repeated lumbar punctures after therapy showed persistently elevated CSF protein but negative cytology. The clinical findings, however, were progressive.

Parenchymal disease was seen in one patient with a history of melanoma, who had an enhancing mass in the cerebellum, seen equally well on standard- and high-dose images. This lesion was resected and found to be a metastasis.

Normal examinations were seen in five patients. Only one of these had a lumbar puncture, and the CSF was normal. These patients were followed clinically, and showed no evidence of leptomeningeal or parenchymal metastatic disease (follow-up 1–13 months, mean 8.5 months).

Discussion

Our data demonstrate the added benefit of high-dose gadolinium-enhanced MRI over standard-dose imaging in the diagnosis of meningeal metastases. The high-dose images improved diagnostic confidence not only by increasing the extent of abnormal enhancement but also by highlighting the nodularity of enhancement as compared with standard-dose images. Confident diagnosis of abnormal leptomeningeal enhancement is made difficult by the presence of enhancing pial veins in the sulci that can mimic enhancing meninges. Thus, demonstrating nodularity may improve diagnostic confidence.

High-dose gadolinium-enhanced MRI has been proposed as a method of increasing sensitivity for parenchymal CNS metastatic disease [6–9]. However, no previous series addressed the value of high-dose gadolinium-enhanced imaging in the diagnosis of leptomeningeal disease.

Unfortunately, the diagnosis of leptomeningeal disease remains difficult. A single lumbar puncture with negative cytology is inadequate to exclude the disease. Most authorities recommend at least three sequential lumbar punctures when suspecting leptomeningeal metastases. Cisternal or C1-2 puncture may be required. However, even multiple spinal punctures may fail to detect the disease in 15–20 % of patients harboring leptomeningeal metastases [1].

Standard-dose gadolinium-enhanced MRI has been used to detect leptomeningeal disease. Even though it is superior to contrast-enhanced CT, the accuracy of standard-dose MRI imaging is limited; reported sensitivities range from 36 % to 71 % [2–5]. These sensitivities may be too high, however, as CSF cytology, the reference examination, is itself lacking in sensitivity.

The use of high-dose imaging for cranial metastases has become less popular not only because of cost considerations but also because of the added sensitivity over standard spin-echo imaging afforded by magnetization transfer imaging. We do not suggest high-dose imaging in all patients referred for brain MRI. However, we do suggest that, when there is strong clinical suspicion of leptomeningeal metastases and standard-dose imaging fails to detect such disease, an additional bolus of 0.2 mmol/kg of gadolinium may be administered with the patient still in the imager, to improve sensitivity. Furthermore, if CSF cytology is persistently negative despite strong clinical suspicion, foci of abnormal leptomeningeal enhancement can be used as a guide for biopsy.

The absolute sensitivity of high-dose imaging for leptomeningeal disease remains unknown. Our series

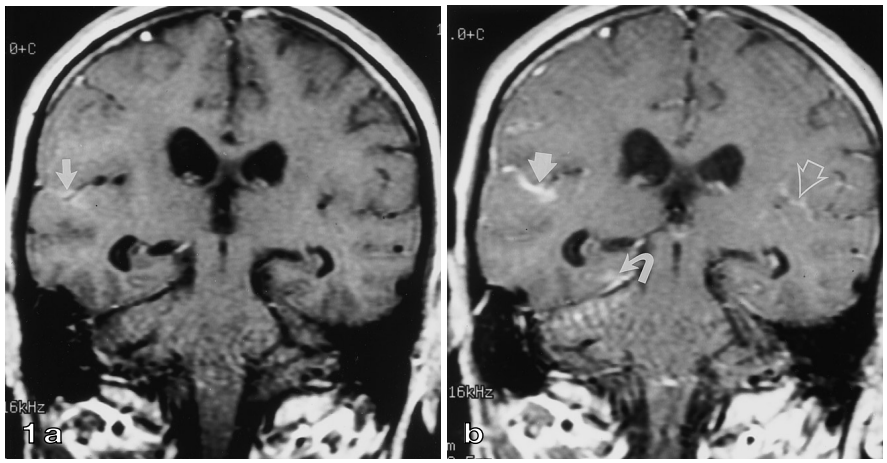

Fig. 1 60-year-old man with CSF cytology revealing lymphoma. **a** Coronal standard-dose gadolinium-enhanced T1-weighted image. Leptomeningeal enhancement was thought normal, although the reader noted possibly abnormal enhancement in the right temporal lobe *(arrow)*. **b** High-dose (0.3 mmol/kg) image. Thick, nodular leptomeningeal enhancement is present along the right sylvian fissure *(arrow)* in the region suspect in **a**. There is also abnormal leptomeningeal enhancement along the medial right temporal lobe *(curved arrow)* and within the left sylvian fissure *(open arrow)*. These latter regions were normal in **a**

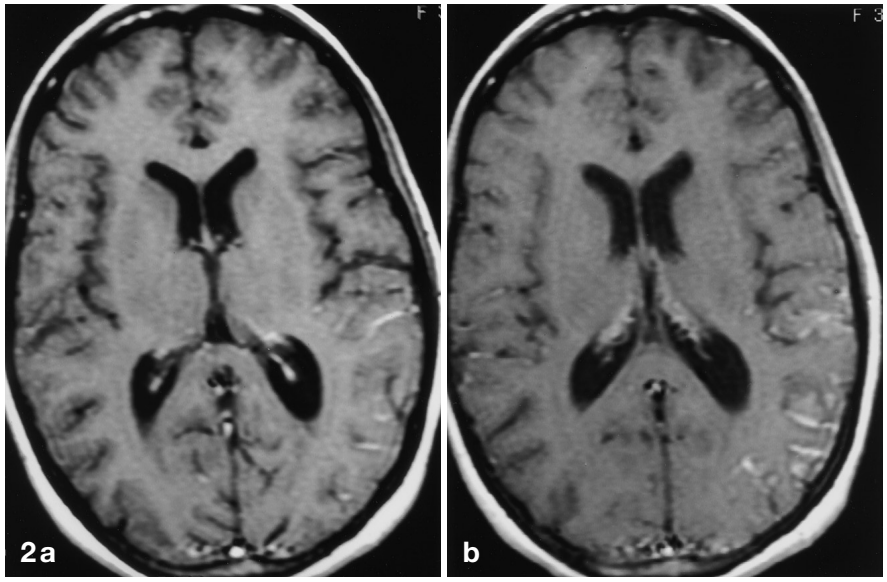

Fig. 2 55-year-old woman with CSF cytology demonstrating metastatic breast carcinoma. **a** Axial standard-dose gadolinium-enhanced T1-weighted image. Thin, linear leptomeningeal enhancement is present in the left posterior temporal region. **b** High-dose (0.3 mmol/kg) image. The abnormal leptomeningeal enhancement is more extensive and nodular in appearance

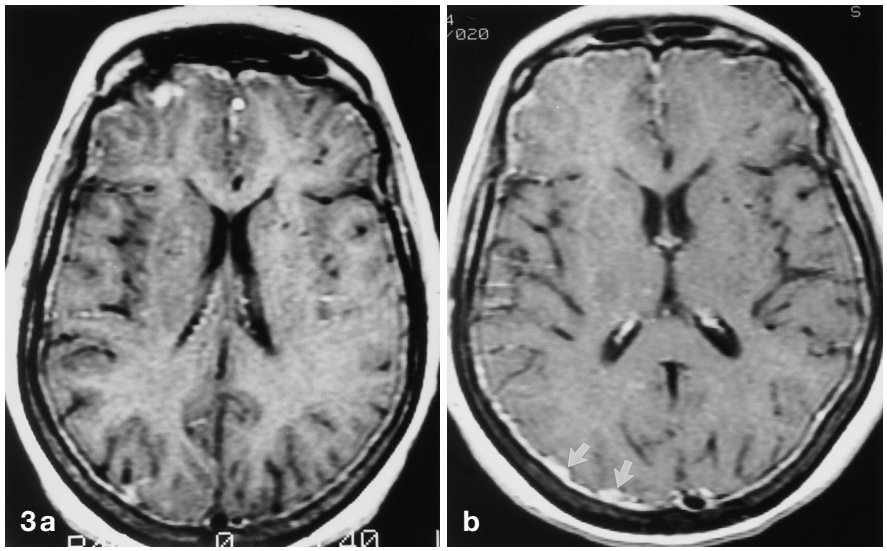

Fig. 3 50-year-old man with metastatic melanoma in whom CSF analysis showed elevated protein but negative cytology. **a** Axial standard-dose gadolinium-enhanced T1-weighted image. Diffuse, linear dural enhancement is present. **b** High-dose image: the dural enhancement appears more nodular *(arrows)* than in **a**

was small, and patients with normal imaging did not undergo the rigorous CSF studies necessary to confirm or exclude disease. While it would have been ideal to perform CSF cytology on all patients, our data suggest that high-dose gadolinium-enhanced imaging is more sensitive than standard-dose imaging.

The significance of pachymeningeal enhancement deserves comment. We and others [10] have noted abnormal enhancement limited to the dura mater with CSF cytology that revealed malignant cells. However, positive CSF cytology in the presence of isolated dural disease is rare; it was seen in only one of 66 patients in the autopsy series reported by Glass et al. [1]. CSF cytology that is positive for metastases indicates that the disease has spread to the leptomeninges; dural metastases alone should not result in positive CSF cytology. This suggests that, in patients with positive CSF cytology and abnormal enhancement limited to the pachymeninges, MRI is failing to show the leptomeningeal component of the disease.

The relative specificity of high-dose images is of theoretical concern. Indeed, we wondered whether the leptomeningeal and dural enhancement seen on the high-dose images was simply dose-related. However, all six patients with dural or leptomeningeal enhancement in this study had definite CSF abnormalities. Furthermore, none of the earlier series with high-dose imaging reported false-positive diagnoses of leptomeningeal disease.

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