Value of pituitary gland MRI at 7 T in Cushing's disease and relationship to inferior petrosal sinus sampling: case report

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Cushing's disease is caused by adrenocorticotrophic hormone (ACTH)–secreting pituitary adenomas, which are often difficult to identify on standard 1.5-T or 3-T MRI, including dynamic contrast imaging. Inferior petrosal and cavernous sinus sampling remains the gold standard for MRI-negative Cushing's disease.

The authors report on a 27-year-old woman with Cushing's disease in whom the results of standard 1.5-T and 3-T MRI, including 1.5-T dynamic contrast imaging, were negative. Inferior petrosal sinus sampling showed a high central-to-peripheral ACTH ratio (148:1) as well as a right-to-left ACTH gradient (19:1), suggesting a right-sided pituitary microadenoma. The patient underwent 7-T MRI, which showed evidence of a right-sided pituitary lesion with focal hypoenhancement not visualized on 1.5-T or 3-T MRI. The patient underwent an endoscopic endonasal transsphenoidal operation, with resection of a right-sided pituitary mass. Postoperatively, she developed clinical symptoms suggestive of adrenal insufficiency and a nadir cortisol level of 1.6 µg/dl on postoperative day 3, and hydrocortisone therapy was initiated. Permanent histopathology specimens showed Crooke's hyaline change and ACTH-positive cells suggestive of an adenoma.

MRI at 7 T may be beneficial in identifying pituitary microadenoma location in cases of standard 1.5-T and 3-T MRI-negative Cushing's disease. In the future, 7-T MRI may preempt inferior petrosal sinus sampling and help in cases of standard and dynamic contrast 1.5-T and 3-T MRI-negative Cushing's disease.

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KEY WORDS 7-T MRI; Cushing's disease; pituitary surgery

ENDOGENOUS Cushing's syndrome is a physical state characterized by excessive blood levels of cortisol. The most common form of endogenous Cushing's syndrome, Cushing's disease, is caused by an adrenocorticotrophic hormone (ACTH)–producing adenoma in the pituitary gland. A pituitary adenoma is responsible for 80%–85% of ACTH-dependent Cushing's syndrome, where ACTH oversecretion causes the adrenal gland to secrete excessive amounts of cortisol.¹⁰ Corticotroph adenomas are often microadenomas, which may be difficult to diagnose due to challenges with the physiological and even pathological findings in these patients. Often the

MRI examination is hampered by the inability to visualize small microadenomas compared with other nonneoplastic pituitary gland lesions.¹ Negative MRI findings may occur in up to 40% of cases of ACTH microadenomas.⁷ For this reason, final diagnosis often relies on bilateral inferior petrosal sinus sampling (IPSS) coupled with MRI (including dynamic contrast-enhanced MRI).¹¹ The treatment of Cushing's disease requires surgical removal of the tumor, which is greatly facilitated by an accurate visual depiction of the lesion. Currently, MRI at 1.5 T is most commonly used, but pituitary microadenomas remain undetected in up to 36%–63% of patients examined with this field

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; GBCA = gadolinium-based contrast agent; IPSS = inferior petrosal sinus sampling; POD = postoperative day; RF = radiofrequency; TSE = turbo spin echo.

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strength.^{1,3,4,9,13} MRI at 3 T has demonstrated increased sensitivity for pituitary microadenomas,¹⁷ and theoretically, even higher field strength of 7 T should result in higher spatial resolution of images, thereby increasing the feasibility of tumor detection. To examine higher MRI field strength in the identification of pituitary microadenomas, we present a case of clinically proven Cushing's disease with pituitary gland MRI at 1.5 T, 3 T, and 7 T, and its relation to IPSS findings.

Case Report

History and Presentation

A 27-year-old woman with a history of primary amenorrhea presented to the USC Pituitary Center following evaluation by an endocrinologist. She previously took oral contraceptive agents for several years, which induced and normalized menstrual periods. However, she stopped taking them and had since only had one period over several months. She reported weight gain and hair loss on her scalp, associated with progressively coarsening hair on her face. She reported easy bruising of the skin, as well as insomnia and anxiety. She denied any history of hypertension or diabetes.

Examination Findings

On physical examination, she was healthy appearing. Her blood pressure was 107 mm Hg/76 mm Hg, and her heart rate was 84 bpm. She was neurologically intact, with lipodystrophy in the supraclavicular and dorsal cervical region, and mild facial plethora. There were no abdominal striae present and no proximal muscle weakness on examination.

Laboratory evaluation demonstrated elevated 24-hour urinary free cortisol excretion at 180 µg (normal 3.5–45 µg/24 hours), and midnight salivary cortisol measurements of 130 and 191 ng/dl (normal < 100 ng/dl). The serum testosterone level was 23 ng/dl. Additional laboratory values included a serum ACTH level of 25.8 pg/ml (normal < 52 pg/ml), and an elevated serum dehydroepiandrosterone (DHEA) level of 483 µg/dl (normal 98.8–340 µg/dl).

An initial pituitary imaging study was performed using 1.5-T MRI, and it showed no evidence of a distinct microadenoma. The patient was referred for IPSS, which showed a strong central to peripheral and right to left gradient. The baseline ACTH level was 560 pg/ml on the right and 15 pg/ml on the left. Fifteen minutes following administration of corticotropin-releasing hormone, IPSS showed ACTH levels of 5906 pg/ml (right) and 313 pg/ml (left), with a peripheral venous ACTH level of 40 pg/ml. The central/peripheral gradient was therefore 148:1 and right/left gradient was 19:1. The patient had normal and symmetric venous sinus anatomy.

Preoperative 3-T and 7-T MRI

Endoscopic endonasal transsphenoidal resection of a presumed pituitary microadenoma was recommended. Under an IRB-approved research protocol and following informed consent, the patient underwent 3-T (Siemens Magnetom Prisma 3 T) and 7-T (Siemens Magnetom Terra 7 T) MRI studies at our institution 2 hours prior to the operation. The 3-T MRI protocol included a pre- and

postcontrast T1-weighted turbo spin echo (TSE) sequence as well as a T2-weighted TSE sequence. The 7-T protocol included a T2-weighted TSE sequence, and pre- and post-contrast (3D) T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE). A single-dose (0.1 mmol/kg) gadolinium-based contrast agent (GBCA) (Dotarem, Guerbet LLC) was administered intravenously. Post-contrast scanning occurred approximately 1 minute after the GBCA was injected, and a dynamic contrast-enhanced scan was not obtained.

Figure 1 shows 1.5-T, 3-T, and 7-T coronal T2-weighted, precontrast T1-weighted, and postcontrast T1-weighted images, with the 1.5-T and 3-T images demonstrating what appears to be a normal pituitary gland. Dynamic MRI was not helpful at 1.5 T and was not performed at 3 T or 7 T. The 7-T postcontrast T1-weighted imaging demonstrates what appears to be an 8-mm right-sided pituitary microadenoma which correlated with the IPSS findings. This 7-T MRI study provided additional support regarding tumor location for the neurosurgeon to proceed to surgery. The 7-T T2-weighted and T1-weighted images demonstrated some asymmetry to the pituitary and very high-resolution visualization of the surrounding brain compared with the 1.5-T and 3-T images. Following contrast administration, there is hypoenhancement on the right side of the pituitary suggestive of a microadenoma. The left side of the sella enhances more avidly, suggesting normal pituitary tissue. There is also some deviation of the pituitary stalk to the left.

Operation and Postoperative Course

The patient underwent an endonasal endoscopic transsphenoidal tumor resection. Following standard sellar and full pituitary gland exposure, and confirmation using MR neuronavigation, a horizontal incision was made in the right pituitary gland and a D dissector was used to dissect out what appeared to be a white microadenoma. Abnormal tissue was sent for permanent pathological examination. The normal pituitary gland was preserved. There was no evidence of intraoperative CSF leak, and no operative complications.

Postoperatively, the patient's initial serum cortisol level was 54.9 µg/dl. Subsequent postoperative day (POD) 1 cortisol levels decreased to 27.9, 13.3, and 11.7 µg/dl. On POD 2, her cortisol levels were 8.7, 5.0, and 2.5 µg/dl. On POD 3, her cortisol levels were 4 and 1.6 µg/dl, and she began to feel nauseated and fatigued and had developed a headache. Her sodium levels were normal. She was prescribed hydrocortisone 20 mg twice daily to treat adrenal insufficiency secondary to surgical excision of her tumor and discharged home the following day.

Histopathological analysis showed abnormal pituitary tissue with focal ACTH positivity and Crooke's hyaline change, indicating prolonged hypercortisolemia. Immunohistochemistry demonstrated focal ACTH-staining cells at the periphery of the sample. Findings were suggestive of an ACTH-secreting adenoma.

The patient had rapid clinical improvement in lipodystrophy and skin bruising. There was a fall in serum cortisol to below 2 µg/dl coupled with symptoms of adrenal withdrawal, compatible with early remission.

FIG. 1. A: Coronal 1.5-T T2-weighted, precontrast T1-weighted, and postcontrast T1-weighted MR images demonstrating what appears to be a normal pituitary gland. **B:** Coronal 3-T T2-weighted, precontrast T1-weighted, and postcontrast T1-weighted MR images also demonstrating what appears to be a normal pituitary gland. **C:** Coronal 7-T T2-weighted, precontrast T1-weighted, and postcontrast T1-weighted MR images demonstrating what appears to be an 8-mm right-sided hypoenhancing pituitary microadenoma (arrow in right panel), which correlates with the results of IPSS. The 7-T MRI study increased the neurosurgeon's diagnostic confidence to proceed to surgery. The left side of the sella demonstrates normal enhancing pituitary, and there is some deviation of the pituitary stalk toward the left. The 7-T T2-weighted image clearly demonstrates considerably higher resolution than the 1.5-T and 3-T images.

The patient gained menstrual function following the procedure. A follow-up 24-hour urinary free cortisol level obtained 5 months after surgery, and after successful weaning from glucocorticoid hormone replacement, showed hormonal remission with a normal level of 22 μg (normal 3.5–45 $\mu\text{g}/24$ hour).

Discussion

The challenge in the diagnosis of Cushing's disease lies in part on the distinction between physiological and pathological elevation of cortisol and a varied phenotype that is often mistaken for Cushing's disease. To date imaging is an ancillary data point partly because MRI is often negative and physicians rely on physiological and ultimately pathological confirmation of a microadenoma. In this case, initial 1.5-T imaging results were inconclusive, and the patient traveled a long distance to be scanned at higher field strengths (3 T and 7 T). When Cushing's disease is suspected and pituitary MRI is inconclusive in the identification of a pituitary lesion, bilateral IPSS is the recommended standard. This method of diagnosis is highly successful in differentiating Cushing's disease from ectopic ACTH-dependent Cushing's syndrome, and may provide useful information regarding laterality in the setting of a normal venous drainage pattern.^{6,12} However, IPSS is a poor predictor of tumor location,^{8,18,19} especially

in children and in cases where venous drainage patterns are asymmetrical.² Furthermore, IPSS is an invasive and costly procedure that is not completely without risk.

In this particular case, 7-T MRI showed evidence of a suspected pituitary microadenoma that was not readily identified on 1.5-T or 3-T MRI, and the 7-T MRI findings correlated well with the IPSS findings. This is concordant with the findings of de Rotte et al., who demonstrated that high-resolution 7-T MRI allows visualization of more lesions than 1.5-T MRI, and the addition of 7-T MRI confirmed an unclear lesion or enabled visualization of an actual lesion that was not visible at 1.5 T.⁵ Although surgical pathology was suggestive but not definitive for an ACTH-secreting adenoma in our case, the patient entered early clinical and laboratory remission requiring cortisol replacement. Nonidentification of a pituitary microadenoma is not uncommon in Cushing's disease and is often due to difficulty with soft microadenomas, transfer and preservation of tissue, and pathology processing technique.^{15,16}

VIBE/SPGR gradient echo T1-weighted sequences have been found to detect microadenomas at a higher rate (15%–30%) than standard spin echo T1-weighted postcontrast images.⁶ In our patient, the VIBE/SPGR gradient T1s and coronal dynamic sequences were also performed at 1.5 T and 3 T.¹⁴ The microadenoma was not visible with these sequences, including spin echo postcontrast T1-sequences with fat saturation at 1.5 T and 3 T.

The sensitivity of spin echo versus gradient echo (VIBE and SPGR) type sequences warrants further discussion. VIBE and SPGR in particular are advantageous for the volumetric dynamic coronal T1-weighted sequences through the pituitary gland. These are now fairly standard sequences on most MRI scanners and are frequently used in the preoperative examination of patients in whom a pituitary microadenoma is suspected. When translating these sequences to 7 T there are several unique challenges due to the effect of changes in T1 relaxation times of different tissues as well as gadolinium contrast. The increased susceptibility and inhomogeneity in the skull base is an added challenge at 7 T. This newest-generation 7-T scanner at our institution takes advantage of a 32-channel receive coil with parallel imaging technology, which allows for reducing susceptibility and also reducing energy/radiofrequency (RF) deposition, allowing for translation of these MRI sequences at 1.5 T and 3 T to possible routine clinical imaging, previously not easily possible at 7 T. Dynamic T1-weighted imaging is also very important at 1.5 T, 3 T, and likely 7 T, as the higher vascularity of normal pituitary tissue will allow differentiation from the less vascular adenoma. The inherent advantage of 7 T in the higher signal-to-noise ratio and spatial resolution should also improve the overall conspicuity of a microadenoma in dynamic T1-weighted imaging of the pituitary.

The important parameters when comparing the 1.5 T, 3 T, and 7 T include the matrix resolution of the image and the slice thickness. Table 1 provides the comparative matrix and slice thicknesses.

Although 7-T MRI is currently still an investigational modality, with improvements in technology, it is likely that it will soon become a clinical tool. Some of the challenges of ultra-high field MRI (7 T and above), which include susceptibility artifact at the skull base, higher RF deposition, and sequence optimization, have been addressed with this current newer generation of 7 T at our institution. With further optimization of the hardware and software, it will be likely that clinical neuroimaging will soon transition from 3 T to 7 T. This particular report is limited by its single-case nature; a study currently underway at our institution will involve a larger series of patients with Cushing's disease, who will have comparative 3-T and 7-T MRI scans with IPSS correlation.

TABLE 1. Comparison of matrix resolution and slice thickness for various sequences of 1.5-T, 3-T, and 7-T MRI

Magnet Strength	Sequence	Matrix Resolution	Slice Thickness (mm)
1.5 T	T1 weighted	205 × 256	2
1.5 T	T2 weighted	288 × 384	2
3.0 T	T1 weighted	205 × 256	2
3.0 T	T2 weighted	288 × 384	2
7.0 T	T1 weighted	320 × 320	0.5
7.0 T	T2 weighted	288 × 384	2

The coronal T1-weighted images obtained with a 7-T scanner have a higher matrix size and smaller slice thickness than corresponding images obtained with a 1.5-T or 3-T scanner. This becomes an important factor for detecting microadenomas.

Conclusions

Pituitary MRI at 7 T presented clearer visualization of a pituitary microadenoma in a patient with confirmed Cushing's disease than 1.5-T and 3-T MRI did, without significant artifact from surrounding bony or sinus anatomy. The 7-T MRI findings also correlated with IPSS findings in this particular case. In the future, 7-T MRI may become more routine and possibly preempt IPSS in patients who have Cushing's disease that is considered MRI negative based on standard 1.5-T and 3-T imaging studies.

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Disclosures

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