Endocrine
DOI 10.1007/s12020-016-1038-y

MINI REVIEW

Pituitary magnetic resonance imaging in Cushing's disease

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Received: 16 April 2016 / Accepted: 24 June 2016

Abstract Adrenocorticotropin-secreting pituitary tumor represents about 10 % of pituitary adenomas and at the time of diagnosis most of them are microadenomas. Transsphenoidal surgery is the first-line treatment of Cushing's disease and accurate localization of the tumor within the gland is essential for selectively removing the lesion and preserving normal pituitary function. Magnetic resonance imaging is the best imaging modality for the detection of pituitary tumors, but adrenocorticotropin-secreting pituitary microadenomas are not correctly identified in 30–50 % of cases, because of their size, location, and enhancing characteristics. Several recent studies were performed with the purpose of better localizing the adrenocorticotropin-secreting microadenomas through the use in magnetic resonance imaging of specific sequences, reduced contrast medium dose and high-field technology. Therefore, an improved imaging technique for pituitary disease is mandatory in the suspect of Cushing's disease. The aims of this paper are to present an overview of pituitary magnetic resonance imaging in the diagnosis of Cushing's disease and to provide a magnetic resonance imaging protocol to be followed in case of suspicion adrenocorticotropin-secreting pituitary adenoma.

Keywords Cushing's disease · MRI · Imaging · Pituitary microadenoma

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Introduction

Adrenocorticotropin (ACTH)-secreting pituitary tumor represents ≈10 % of pituitary tumors [1, 2] and on diagnosis most are microadenomas (<10 mm in largest diameter) [3]. Transsphenoidal surgery is the first-line treatment for Cushing's disease (CD) and accurate localization of the tumor within the gland is essential for selectively and successfully tumor removal. Magnetic resonance imaging (MRI) of the pituitary gland is currently the imaging procedure of choice in CD patients [4, 5]. Although the sensitivity of conventional MRI for ACTH-secreting tumors varies widely among different authors, it is generally accepted that these tumors are not correctly identified in about 30–50 % of cases [4, 6–13]. In fact, detection of ACTH-secreting microadenomas is not always possible by MRI: almost 50 % of these tumors have size <5 mm [14],

Published online: 19 July 2016

they are frequently located in the pituitary gland central or ventral portion and exhibit signal and enhancing characteristics similar to those of normal pituitary parenchyma, resulting in false negative [15]. Moreover, many false positive results were described in the identification and localization of these tumors [16].

Because of low accuracy of standard MRI, several centers are used to perform inferior petrosal sinus sampling (IPSS) in order to localize ACTH-secreting tumors [17]. Although IPSS has high diagnostic accuracy, it is an invasive and expensive test and is not widely available. Several recent studies were performed with the purpose of better localizing the ACTH-secreting microadenomas through the MRI use of specific sequences, reduced contrast medium dose and high-field technology [18–20]. Therefore, an improved imaging technique for pituitary disease is mandatory and a specific MRI protocol, to be used in the suspect of an ACTH-secreting tumor, can be helpful both in the routine clinical practice and in the management of pharmacological trials. The aims of this review are at presenting an overview of pituitary MRI diagnosis and at providing an MRI protocol to be followed in case of suspect of ACTH-secreting pituitary tumors.

1.5 Tesla MRI in CD

1.5 Tesla MRI is commonly used for pituitary imaging. Standard MRI includes T1-weighted (w) spin-echo (SE) sequences performed in both coronal and sagittal planes through the pituitary fossa, repeated after administration of intravenous gadolinium contrast medium, and associated with a T2-w sequence in the coronal plane. The lesion responsible for CD usually appears as a focal area of <10 mm with a lesser enhancement on T1-w imaging following contrast administration, hyperintense or hypointense on T2 imaging as compared to the normal pituitary gland [6, 9].

High spatial detail is critical and should be achieved through the use of thin slices (2–3 mm or smaller), a fine matrix size (256×512 or more), and a relatively small field of view (FOV) [21]. The FOV, which optimally focuses on pituitary gland rather than the entire brain, appears to be crucial for microadenomas detection, probably because a large FOV has less resolution for a given matrix. In fact, the resolution resulted to be superior in a pituitary study performed with a FOV of 12×12 cm as compared to a FOV of 18×18 cm for the same matrix [15]. Different crucial parameters in detecting microadenomas are repetition time (TR) and echo time (TE). TR and TE values in the range of 500–700 and 15–25 ms, respectively, are recommended for pituitary imaging [21]. However, Chowdhury et al. reported better results in detecting pituitary ACTH-secreting tumors with shorter TR (400 ms) and TE (10.3 ms) [15].

The development of dynamic pituitary MRI with the use of multiple coronal dynamic sequences following gadolinium intravenous injection increases sensitivity and specificity. Friedman et al. reported that dynamic MRI showed a pituitary lesion in 96 % of patients with a biochemical diagnosis of ACTH-dependent CD. Therefore, the sensitivity in finding a pituitary lesion in suspected CD patients with 1.5 Tesla dynamic MRI resulted to be higher than the 50–60 % rate reported for non-dynamic MRI [22].

Sagittal and coronal T1-w fat saturated post gadolinium sequences are also useful in pituitary imaging for a better delineation of pituitary lesions and pituitary postoperative evaluation [23].

Another important parameter potentially affecting MRI sensitivity is the contrast medium dose. The recommended dose of paramagnetic contrast agent in MRI imaging for most intracranial diseases is 0.1 mmol/kg [24]. However, studies performed both on pituitary tumor and in normal gland reported no significant loss of sensitivity using a 50 % reduction of the usual dose of contrast medium [25, 26]. Smaller pituitary lesions can be recognized generally for their reduced enhancement in comparison with contiguous normal gland, in particular immediately after contrast. The administration of full contrast dose in pituitary MRI causes a greater enhancement of glandular parenchyma, which results in increased signal intensity of the normal pituitary tissue. In small tumors this may make difficult the differentiation between the pituitary tumor from adjacent normal tissue. In this context, the use of half dose can be considered attractive, because a smaller contrast dose produces less contrast gland enhancement. However, data on this topic are limited and discordant in patients with CD. A retrospective study in patients receiving half-dose (0.05 mmol/kg, 18 patients), standard dose (0.1 mmol/kg, nine patients), and double dose (0.2 mmol/kg, 13 patients) for detection of microadenomas [27], demonstrated a clear correlation between infused contrast dose and enhancement of the pituitary or the microadenoma. Although the calculated contrast ratios between gland and microadenoma were similar in the three different groups, the absolute signal difference between pituitary and microadenoma was linearly related to pituitary gland enhancement, so determining a greater signal difference with a higher contrast medium dose levels. The difference in signal between gland and lesion is considered a crucial parameter for optimum detection of pituitary microadenoma. However, this study included only one patient with CD and two others with "suspected CD". All three patients received a half-dose pituitary MRI protocol. Another study performed using dynamic 3-T MRI supported the utility of the half-dose protocol for better detecting ACTH-secreting microadenoma [20].

The signal-to-noise ratio is one of the most important measures of the performance of a MRI system, frequently

Clinical and biochemical findings suspicious for an ACTH-secreting pituitary adenoma

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Pituitary MRI

	Coil Type	Plane	Mode	Pulse Sequence	TE	TR	FOV	Slice Thickness	Matrix Size
SAGITTAL T1	Head	SAG	2D	SE	10.3 ± 0.5 ms	400 ms	12-14 cm	1-1.5 mm	≥ 256x512
CORONAL T1	Head	COR	2D	SE	10.3 ± 0.5 ms	400 ms	12-14 cm	1-1.5 mm	≥ 256x512
CORONAL T2	Head	COR	2D	SE	100-120 ms	3000-4000 ms	14-18 cm	1-1.5 mm	≥ 256x512
CORONAL DINAMIC	Head	COR	2D	SE	17 ms	400 ms	12-14 cm	1-1.5 mm	256x192
SAGITTAL T1 POST FS	Head	SAG	2D	SE	10.3 ± 0.5 ms	400 ms	12-14 cm	1-1.5 mm	≥ 256x512
CORONAL T1 POST FS	Head	COR	2D	SE	10.3 ± 0.5 ms	400 ms	12-14 cm	1-1.5 mm	≥ 256x512
CORONAL VI-SGE	Head	COR	3D	GE	3.3 ms Flip angle 15°	10-15 ms	16 cm	1 mm	256x205

Fig. 1 A recommended pituitary MRI protocol to be adopted in patients with clinical and biochemical findings suspicious for an ACTH-secreting pituitary adenoma. These parameters should be maintained in post-contrast medium acquisitions. *cm* centimetres, *COR* coronal, *FOV* field of view, *FS* fat saturated post gadolinium, *GE* gradient echo, *ms* milliseconds, *SAG* sagittal, *SE* spin echo, *TE* echo time, *TR* repetition time, *VI-SGE* volume interpolated-spoiled gradient echo sequence

calculated by the difference in signal intensity between the area of interest and the background. This parameter determines how grainy the image appears, the more grainy, the less the signal-to-noise ratio. The use of a three-dimensional (3D) acquisition with very thin sections (up to 1 mm) presents important advantages as compared to conventional SE sequences, including high signal-to-noise ratio [28]. The 3D spoiled gradient recalled acquisition in the steady state (SPGR) sequence is a MRI technique characterized by superior soft-tissue contrast compared with T1-w SE technique. An optimized SPGR acquisition with thin-slice imaging has been reported to substantially improve imaging resolution and the diagnosis of ACTH-secreting microadenomas. In comparison with the T1-w SE sequence, SPGR demonstrated superior sensitivity (80 vs. 49 %) but a double false positive rate (8 vs. 4 %) [18]. However, overall diagnostic accuracy resulted higher for post-contrast SPGR sequence as compared to post-contrast SE sequence (74 vs 48 %). The utility of 3D acquisition in CD has been confirmed in another retrospective study performed on 36 patients with CD, showing that the volume interpolated-spoiled gradient echo sequences have a greater sensitivity (87 %) than dynamic contrast SE sequences (66 %) [29].

Fig. 1 describes the recommended pituitary MRI protocol to be adopted in patients with clinical and biochemical findings suspicious for CD.

3 Tesla MRI in CD

Spatial resolution in MRI depends upon several parameters, which can be increased by two methods: (1) by acquiring more data and signal averaging and consequently prolonging the acquisition time and increasing the motion artifacts; (2) by increasing the strength of the main magnetic field [30].

3 Tesla operating machine allows greater spatial resolution and reduced acquisition time, due to its increased MRI

signal, in addition to improved tissue enhancement after intravenous gadolinium. As a matter of fact, 3 Tesla MRI compared to 1.5 Tesla MRI showed a higher resolution and a proper image quality with clear advantages in detecting pituitary tumors. In particular, 3 Tesla MRI allows a better localization of pituitary microadenomas, an exceptional delineation of parasellar anatomy and a superior prediction of cavernous sinus invasion [31, 32]. This is especially true when using T1-w 3D sequences, which offer improved quality images by minimizing susceptibility artifacts in the sellar and parasellar region associated with a reduced slice thickness (1–2 mm) [33].

In a preliminary study [33] performed in five patients with endocrine and clinical confirmation of CD, 3 Tesla MRI further delineated and/or newly demonstrated a pituitary microadenoma in three cases, even though the findings were equivocal in the remaining two cases. In comparison with 1.5 Tesla MRI, the 3 Tesla MRI predicted two cases correctly, two equivocally, and one incorrectly. In a 11-year-old CD patient with negative 1.5 Tesla pituitary MRI, a 3-mm less-enhanced lesion was clearly identified in the left side of the anterior pituitary by 3 Tesla MRI using the SPGR sequence [19]. A 3 Tesla MRI was performed with and without the administration of ovine corticotropic releasing hormone (o-CRH) in 23 patients presenting a clinical and biochemical evidence of CD, with no or equivocal lesions on the pituitary 1.5 Tesla MRI [34]. CRH administration should increase enhancement and presumably improve MRI sensitivity and specificity. Both 3 Tesla MRI with and without o-CRH stimulation resulted significantly more sensitive for detection of pituitary microadenomas rather than 1.5 Tesla MRI, with a sensitivity of 67–70 % in comparison with 30 %; there was no difference between the 3 Tesla and the 3 Tesla with o-CRH stimulation for any of the pulse sequences. Another study [35] compared the diagnostic accuracy of 3 Tesla MRI vs. 1.5 Tesla MRI in T1-w post-gadolinium sequences in detection of ACTH-secreting microadenomas and GH-secreting microadenomas, in 24 patients with biochemical evidence of CD (19 cases) or acromegaly (5 cases). The imaging diagnosis was correlated with subsequent surgical and histological findings. High-field MRI was associated with a higher number of positive radiological reports with four diagnoses of pituitary adenoma and one suspected case, which was negative on 1.5 Tesla. Sensitivity of positive MRI report for histologically demonstrable adenoma was 54 % at 1.5 Tesla and 85 % at 3 Tesla. Despite increased sensitivity with high field strength imaging, specificity was 75 % for both techniques.

Interestingly, half-dose contrast agent for dynamic 3 Tesla MRI seems to increase the sensitivity of detecting ACTH-secreting pituitary tumors. Portocarrero-Ortiz et al. [20] performed a second 3 Tesla MRI using only half dose of gadopentetate dimeglumine (0.05 mmol/kg) in eight patients with clinical and biochemical diagnosis of CD but a previous 3 Tesla MRI negative for tumor localization using full-dose contrast material. After dynamic half-dose MRI, microadenomas were detected in all cases. Transsphenoidal surgery was performed in seven patients and confirmed the diagnosis and localization at MRI. The other patient was submitted to petrosal sinus sampling that confirmed ACTH-secreting pituitary adenoma.

Although 3 Tesla MRI offers a better signal-to-noise ratio compared to 1.5 Tesla MRI, high-field imaging is not free of artifacts. Skull base as sellar and parasellar regions are susceptible of artifacts because of soft tissue, air and bone interface. It creates lack of homogeneity of the magnetic field, anatomical distortion, and potential pituitary lesions obscuration, particularly using higher-field-strength MRI system. Three-dimensional fast spin-echo (FSE) techniques are less susceptible to artifacts. Lien et al. [36] conducted a retrospective study on 91 patients who underwent to 3 Tesla MRI for pituitary lesions. Two independent neuroradiologists assessed MRI imaging assigning the features to a grading score. The infundibulum, the cavernous sinuses, the degree of conspicuity of a lesion and confidence in excluding a lesion were visualized significantly better on 3D FSE for both readers in comparison with 2D T1 FSE sequence. Regarding optic apparatus, reader A found statistically significant differences, whereas reader B did not find statistically significant differences. Overall preference favored 3D FSE cube imaging over 2D FSE. 3D imaging was significantly better than 2D imaging in detection of small pituitary lesions and parasellar region imaging was more clearly delineated with minimal artifact.

Several reports support the use of contrast-enhanced 3 Tesla MRI for CD with negative or equivocal 1.5 Tesla MRI. However, most of these studies compared the diagnostic accuracy of 3 Tesla MRI (performed with the 3D protocol) vs. 1.5 Tesla MRI (performed with a standard protocol). Therefore, future studies should be aimed at comparing the detection rate of the pituitary 3 Tesla and 1.5 Tesla MRI using the same imaging protocol, in order to confirm the better diagnostic accuracy of high-field strength MRI in patients with clinical and biochemical diagnosis of CD.

Future perspectives and conclusion

Recent technological advances, such as ultra-high-field-strength MRI and integrated positron emission tomography (PET)/MRI systems, may represent in future new exciting imaging modalities to study CD.

De Rotte et al. [37] tested a 7 Tesla MRI protocol to visualize the pituitary gland in 10 healthy volunteers and in

5 patients with clinical and biochemical suspicion of a microadenoma. 7 Tesla MRI (in 9 of 10 healthy volunteers) demonstrated high resolution and highly detailed images with an overall good quality of the T2-w turbo spin-echo (TSE) sequence and the T1-w TSE sequence. In 4 of 5 patients with pituitary tumor suspicion, a microadenoma was identified, and histological examination after surgery confirmed the presence of an ACTH-secreting microadenoma. In a recent study the same group evaluated the detection of pituitary lesions at 7.0 Tesla compared to 1.5 Tesla MRI in 16 patients with clinically and biochemically proven CD. In five patients, both the 1.5 Tesla and 7.0 Tesla MRI permitted detection of a lesion on the correct side of the pituitary gland. In three patients, 7.0 Tesla MRI visualized a lesion on the correct side of the pituitary gland, while no lesion was visible at 1.5 Tesla MRI. In one patient only 1.5 Tesla MRI correctly detected the pituitary lesion. The interobserver agreement for lesion detection was good at 1.5 Tesla MRI ($\kappa = 0.69$) and 7.0 Tesla MRI ($\kappa = 0.62$) [38]. Therefore, 7 Tesla MRI may provide new perspectives when used as a second-line diagnostic examination in the specific context of CD.

The integration of PET and MRI into a hybrid system represents another innovative diagnostic technology with potential applications in the diagnosis of CD. In a preliminary study of 35 patients, Ikeda et al. [39] reported a better diagnostic accuracy for diagnosing ACTH-secreting pituitary microadenoma with the association between PET and 3 Tesla MRI (methionine-PET/MRI: 100 %; FDG-PET/MRI: 73 %) than with superconductive MRI (accuracy: 40 %).

In conclusion, 1.5 Tesla MRI is commonly used for pituitary imaging in the clinical practice. An optimal MRI protocol can increase the detection of ACTH-secreting pituitary microadenomas. However, very small microadenomas often remain undetected. 3 Tesla MRI is increasingly available worldwide and might be of particular clinical utility in patients with negative or indeterminate results on a 1.5 Tesla MRI. High-field-strength MRI appears to be a promising tool for the diagnosis of CD. However, it is important to consider that the higher spatial resolution of ultra-high-field-strength pituitary gland MRI can increase the risk of false positive, considering that incidentalomas are present in approximately 10–20 % of general population [40].

Acknowledgments This review is part of the "Altogether to Beat Cushing's Syndrome Group" led by Prof Annamaria Colao, which aims at increasing the knowledge on Cushing's Syndrome. The authors would like to acknowledge all the Collaborators of this project: Albani A., Albiger N., Ambrogio A., Arnaldi G., Arvat E., Baldelli R., Barbot M., Boscaro M., Campo M., Cannavò S., Canu L. Cappabianca Paolo, Castinetti F., Cavagnini F., Cavallo L.M., Chiodini I., Ciresi A., Cirillo S., Cocchiara F., Colao A., Corsello S.M., Cozzolino A., Damiani L., De Leo M., De Martino M.C., Farese A., Feelders R., Ferone D., Gatto F., Graziadio C., Grimaldi F., Iacuaniello D., Isidori A.M., Karamouzis I., Lenzi A., Loli P., Mannelli M., Mantovani G., Marcelli G., Marzullo P., Minniti G., Palmieri S., Paragliola R.M., Pasquali R., Pecori Giraldi F., Pivonello C., Pivonello R., Reincke M., Sbardella E., Scaroni C., Simeoli C., Spada A., Stigliano A., Tortora F., Toscano V., Trementino L., Vitale G., Zampetti B., Zatelli M.C., and Zhukouskaya O.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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