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A modified protocol using half-dose gadolinium in dynamic 3-Tesla magnetic resonance imaging for detection of ACTH-secreting pituitary tumors

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Abstract ACTH-secreting tumors represent 10% of functioning pituitary adenomas, and most of them are microadenomas. It is generally accepted that only half of these tumors are correctly identified with current magnetic resonance imaging (MRI) techniques. The objective of the paper is to report a method for detecting suspected ACTH-secreting pituitary tumors undetectable by conventional dynamic MRI using dynamic 3-Tesla MRI (3T MRI) and half-dose gadopentetate dimeglumine (0.05 mmol/Kg). Eight patients were included (5 men and 3 women) with a mean age of 29.12 years. Each of them had a confirmed diagnosis of Cushing disease and a negative dynamic MRI for microadenoma using full-dose gadopentetate dimeglumine. A second MRI was then performed using only half the usual dose of contrast material. Images from the second MRI where compared with the first study. Microadenomas were detected in 100% of the patients using a half dose of the contrast. All were recognized on the basis of the presence of a hypointense nodular lesion surrounded by normal contrast-enhanced tissue. Six patients were submitted to surgery, and the results were confirmed by immunohistochemistry in all of them. The remaining subject had a sinus sample catheterization coincident with the MRI results. Conclusion: A half dose of dynamic resonance imaging contrast material increases the sensitivity of MRI detection of ACTH-secreting pituitary tumors.

Keywords ACTH pituitary tumors · Half-dose gadolinium · Dynamic MRI

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Introduction

ACTH-secreting tumors constitute 10% of functioning pituitary adenomas [1, 2], and most of them are microadenomas that are only clinically evident by their abnormal hormonal production [3]. The sensitivity of magnetic resonance imaging (MRI) for microadenoma detection is over 85% with conventional techniques [4–6]. Dynamic MRI improves the sensitivity by 5–10% [7]. However, microadenoma detection is not always possible by this method due to strong generalized glandular enhancement after contrast material administration, which makes it difficult to differentiate microadenomas from normal glandular tissue [8]. ACTH-secreting tumor identification is even more difficult due to their localization and size (frequently ventrally located, and almost 50% of ACTH-secreting tumors measure less than 5 mm) [9]. Although the sensitivity of MRI for ACTH-secreting tumors varies widely among different authors, it is generally accepted that these tumors are correctly identified only half of the time [9, 10]. Traditional protocols for dynamic MRI consist of five sets of images obtained after the administration of gadopentetate dimeglumine at a dose of 0.1 mmol/Kg [11]. We propose using half-dose gadopentetate dimeglumine (0.05 mmol/Kg) for dynamic 3-Tesla MRI (3T MRI) when

ACTH-secreting pituitary tumors are suspected as an improved method of tumor identification.

Patients and methods

Eight patients were included in this report, all of whom had a biochemically confirmed diagnosis of Cushing disease [9, 12]. Three patients were submitted to petrosal sinus sampling (PSS). As part of the usual study protocol, a dynamic 3T MRI scan using full-dose contrast material was performed, and it was negative for tumor localization in all patients included in this report. A second MRI using our proposed protocol was then scheduled.

Dynamic MRI

Our dynamic MRI method consisted of a set of three fast spin echo (FSE) T1- and T2-weighted coronal images before gadolinium administration.

Afterwards, one-half dose of contrast material (0.05 mmol of gadopentetate dimeglumine salt at 0.1 ml/kg) was administered, and a set of FSE T1-weighted images was obtained immediately and every 30 s until six total cycles were completed. All MRI scans were performed on a 3-T MRI system (Signa Excite; General Electric, Milwaukee, Wisconsin, USA) with an 8-channel head coil. The acquisition parameters were as follows: T1-weighted 2 mm thick coronal FSE images, 400/11.1/2 (TR/TE/excitations) were obtained by using a 18 × 18 FOV, a 224 × 192 matrix, and an interslice gap of 0.0 mm; T2-weighted 2 mm thick coronal FSE images, 2950/81.6/2 (TR/TE/excitations) were obtained by using a 20 × 20 FOV, a 256 × 224 matrix, and an interslice gap of 0.0 mm.

Images from the half-dose dynamic MRI were compared with the first study by two independent neuroradiologists blinded to the clinical diagnosis and not included in the authorship of this report. The criterion for the identification of a microadenoma was the presence of a <10 mm focal area inside the anterior hypophysis with different signal intensity with respect to the rest of the gland in T1-weighted or T2-weighted images or after contrast material administration.

In patients submitted to surgery, immunohistochemistry was performed for tumor confirmation, and the results were compared with the MRI findings. PSS was also compared with the MRI findings.

Fig. 1 Comparative coronal 3-Tesla MRI images of pituitary glands of five patients with Cushing disease. (**a**,**b**,**c**,**d**,**e**). *First and second column* show simple T1- and T2-weighted images. *Third column* shows the same slices after administration of full contrast material and the *fourth column* show patients after administration of half-dose gadolinium: a focal area of low signal intensity is clearly seen in the pituitary with a different pattern of enhancement with respect to the normal gland (*white arrowheads*) ▶

Results

The eight patients in this study were five men and three women with a mean age of 29.12 years (range 9–44 years). Table 1 shows the clinical and biochemical characteristics of the subjects included in this report.

After dynamic half-dose MRI, microadenomas were detected in 100% of the patients. All (8/8) were isointense in non-enhanced T1-weighted images. In T2-weighted images, (5/8) were hypointense, one was hyperintense, and two were isointense (Table 2). After administration of contrast media, they all showed a nodular focus of distinct enhancement with respect to normal contrast-enhanced tissue. The average diameter was 5.5 mm.

In the first three cases, PSS was performed and showed coincidence with the side previously detected by dynamic half-dose MRI. Figure 1 shows images from five patients comparing the full-dose contrast material protocol with the modified protocol. Figure 2 shows two patients complete dynamic MRI with half-dose gadolinium.

Transsphenoidal surgery was performed in seven patients. Positive immunohistochemistry for ACTH was found in all cases and surgical findings showed coincidence with MRI findings in all patients. The other patient had a

Table 1 MRI findings compatible with pituitary microadenomas in our patients

Patient	Localization	Size	T1-weighted (pre-contrast)	T2-weighted (pre-contrast)	After half-dose gadolinium in dynamic MRI
1	Left	3.9 × 3.8 mm	Isointense	Isointense	Hypointense, PE
2	Right	5.7 × 5.6 mm	Isointense	Isointense	Hypointense, PE
3	Central	6.1 × 5 mm	Hypointense	Hyperintense	Hypointense, CE
4	Right	5.6 × 5.4 mm	Isointense	Hypointense	Hypointense, PE
5	Left	6.3 × 5.8 mm	Isointense	Hypointense	Hypointense, PE
6	Left	5.8 × 7.4 mm	Isointense	Hypointense	Hypointense, PE
7	Left	5.6 × 4.6 mm	Isointense	Hypointense	Hypointense, PE
8	Left	5.1 × 4.4 mm	Hypointense	Hypointense	Hypointense, PE

PE peripheral enhancement, *CE* central enhancement, *mm* millimeters

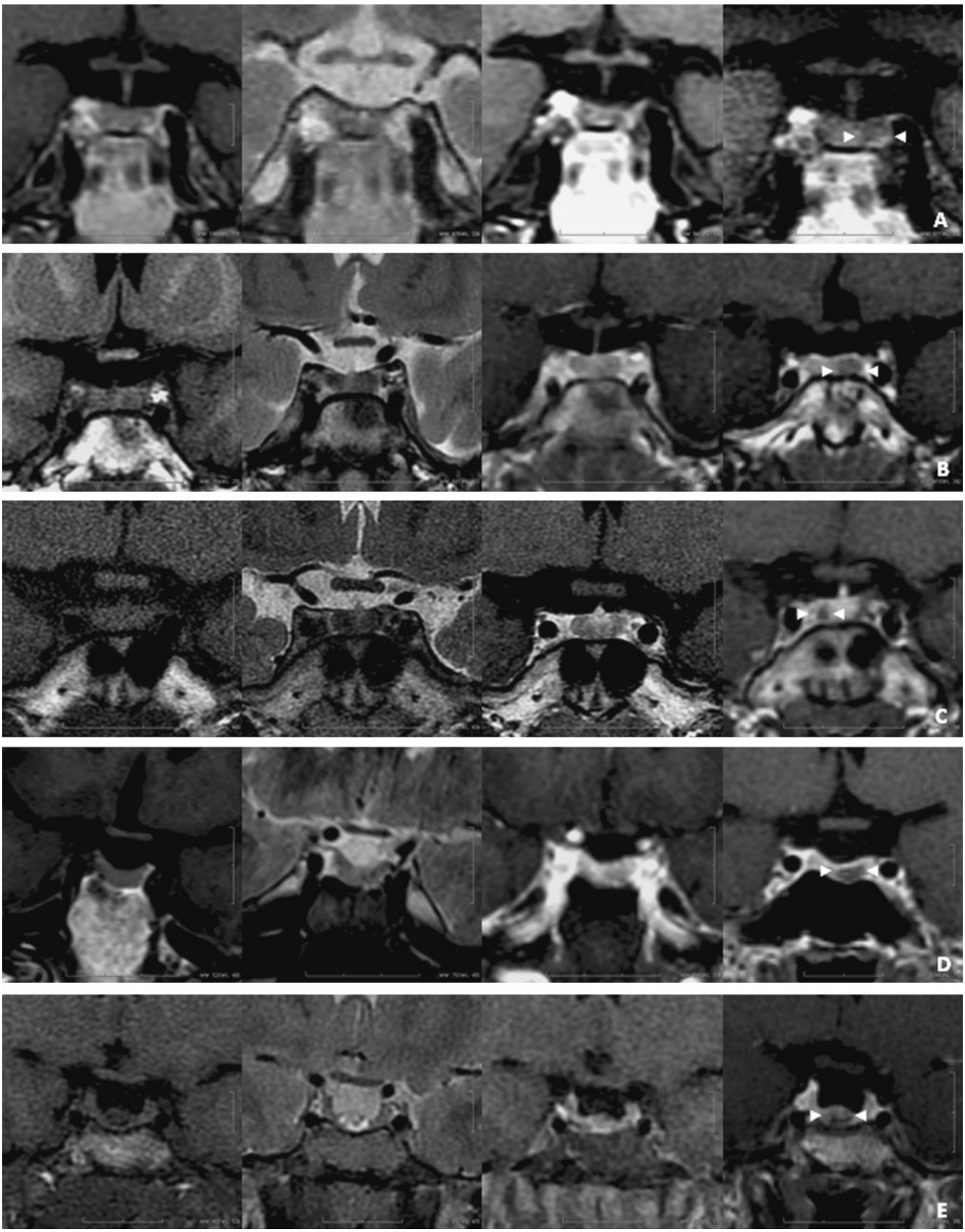

A
B
C
D
E

Table 2 Clinical and biochemical characteristics of patients described in this report

Patient	Age	Gender	ACTH level (pg/ml)	UFC (mcg/24 h)	Weight (kg)	Height (m)
1	9	M	43.7	648	30	1.12
2	44	F	45	521	55	1.42
3	39	F	61.7	143	77	1.5
4	12	M	40.6	646	88	1.42
5	18	M	77	–	87	1.78
6	34	F	110	494	81	1.55
7	34	M	180	892	88	1.77
8	43	M	56	–	76	1.72

ACTH adrenocorticotropic hormone

positive PSS confirming the diagnosis and the localization of the tumor. PSSs of all three patients showed a correlation with the MRI findings using half-dose contrast material.

Fig. 2 Dynamic MRI after administration of half-dose contrast material. It shows the same slice throughout six timed sequences in two different patients (**f**,**g**). A focal area of low signal intensity with a different pattern of enhancement with respect to the normal gland is seen in the pituitary gland (*white arrowheads*) ▶

Discussion

Detection of pituitary adenomas by imaging techniques has always been problematic. ACTH secreting adenomas are frequently found in the central and ventral aspects of the gland, and almost 50% of these tumors measure less than 5 mm [13]. PSS is currently the gold standard for diagnosis, but it remains a complex and expensive method that carries risks and requires highly trained personnel. That is why MRI has been considered for the last two decades to be the method of choice for detecting ACTH-secreting tumors. However, there are still patients in whom tumors cannot be detected even with PSS [14, 15]. In our series, all the MRI studies successfully detected pituitary adenomas. All submitted to surgery (7/8) were confirmed by positive immunohistochemistry, leaving no doubt of the accuracy of the method. As successful treatment for ACTH-secreting adenomas requires precise localization, improvements in imaging techniques result in significant advances in the work-ups of these patients.

Using half-dose contrast material was previously proposed by Davis et al. in 1991. In their study, they found that a half dose of gadopentetate dimeglumine contrast material was as effective as a full dose for identifying micro- and macroadenomas [16]. 3-T MRI using half-dose contrast has shown better sensitivity for brain tumors than 1.5 Tesla [17].

No previous studies have reported using half-dose contrast material in dynamic 3T for pituitary microadenoma detection.

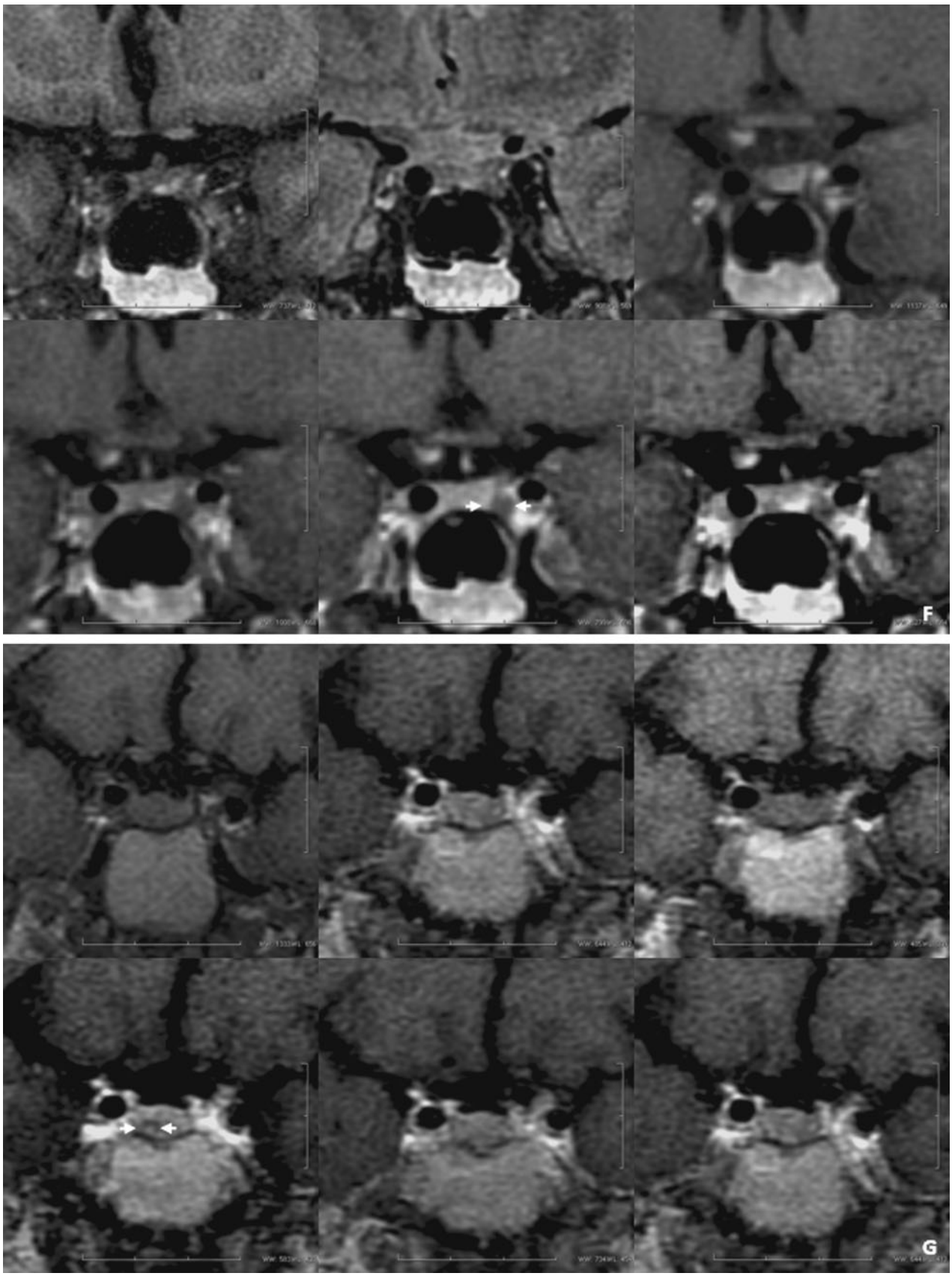
Full-dose contrast probably produces a greater enhancement of glandular parenchyma, which results in increased signal intensity from the normal pituitary tissue. This makes it more difficult to differentiate the pituitary tumor from adjacent normal tissue. Using half-dose contrast produces less contrast enhancement of the gland, allowing better discrimination of abnormal tissue, which manifests as hypointense zones within the pituitary.

Several alternative methods have been proposed to increase the sensitivity of the detection of ACTH-secreting adenomas, most of them with inconsistent results. Recently, corticotrophin releasing hormone (CRH) stimulation was used as a method for improving the detection of ACTH- secreting pituitary tumors [18]. No differences were found between the traditional method and this new method using CRH. Spoiled gradient-recalled acquisition in the steady state (SPGR) has also proven to be more effective than conventional MRI for detecting these tumors, but not enough for it to be adopted as the routine procedure [10]. In this report, all the patients submitted to the study already had a negative conventional dynamic MRI; therefore, they represent a sample of patients where no diagnosis could be established with traditional methods. This emphasizes the importance of this report.

The main limitation of this report is the number of patients included. In is not intended by the authors to demonstrate the sensitivity and specificity of the method, but to report an important upgrade in the MRI protocol that could improve sensitivity for microadenomas detection. New prospective studies must be conducted in order to confirm results here described. Tumor localization prior surgery increases possibilities of success during the procedure and curation of patients with no need of further complementary treatments.

Conclusions

Half-dose contrast material for dynamic 3T MRI increases the sensitivity of detecting ACTH-secreting pituitary tumors.


F
G

Prospective studies must be conducted to confirm results described in this report.

Disclosure statement The authors have nothing to disclose.

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