



Discover Generics

Cost-Effective CT & MRI Contrast Agents



FRESENIUS
KABI

WATCH VIDEO

AJNR

The accuracy of CT and MR evaluation of the sella turcica for detection of adrenocorticotrophic hormone-secreting adenomas in Cushing disease.

M Buchfelder, R Nistor, R Fahlbusch and W J Huk

AJNR Am J Neuroradiol 1993, 14 (5) 1183-1190

<http://www.ajnr.org/content/14/5/1183>

This information is current as
of June 14, 2025.

The Accuracy of CT and MR Evaluation of the Sella Turcica for Detection of Adrenocorticotrophic Hormone–Secreting Adenomas in Cushing Disease

Michael Buchfelder, Raymond Nistor, Rudolf Fahlbusch, and Walter J. Huk

PURPOSE: To document the accuracy of CT and MR of the sella turcica for detecting adrenocorticotrophic hormone-secreting adenomas in Cushing disease. **METHODS:** The radiologic findings of the sella turcica prior to transsphenoidal surgery are reviewed in 141 patients who had biochemical evidence of pituitary-dependent Cushing disease. Axial thin-collimation CT scans with sagittal and coronal reformations before and after contrast enhancement were obtained in 125 patients. Seventy-eight patients had MR examinations with a 1.5-T superconducting magnet. In 11 of the patients gadolinium-enhanced MR scans were also obtained. The preoperative interpretation of the imaging studies was correlated with the surgical findings and patient follow-up. **RESULTS:** The sella turcica was enlarged in 43 cases (30%). In 125 patients reformatted or direct coronal thin-collimation CT scans were available. Seventy-eight of the patients had MR. In the 12 patients with pituitary macroadenomas, the accuracy of CT ($n = 10$) and MR ($n = 10$) in respect to detection of the lesion was 100%. Of the 98 microadenomas assessed by CT, 47 (48%) were directly depicted as distinct hypodense lesions. In only 31 of 73 cases (42%), however, could CT predict the precise anatomic location and extent of the lesions. Only patients in whom the hypercortisolism was corrected by later surgery were considered for the correlation analysis. Of the 52 microadenomas assessed by MR, 28 (53%) were directly depicted as distinct lesions of reduced signal intensity on T1-weighted images, and in only 21 of 41 cases (52%) did MR show good correlation to the surgical findings. Some degree of partially empty sella was found in 22% of the patients. **CONCLUSIONS:** Although both the sensitivity and the diagnostic accuracy of imaging methods of the sella turcica have been considerably improved in comparison with previous reports, they still provide only a minor contribution to the diagnosis and differential diagnosis of Cushing syndrome.

Index terms: Sella turcica, magnetic resonance; Sella turcica, computed tomography; Adenoma; Cushing disease

AJNR 14:1183–1190, Sep/Oct 1993

Adrenocorticotrophic hormone (ACTH)-secreting pituitary adenomas causing Cushing disease were originally described to be minute tumors (1). Neurosurgical experience gained from numerous sella explorations has confirmed that they rarely attain a space-occupying character (2–5). The problems associated with neuroradiologic evaluation

of the sella turcica in this rare kind of pituitary hypersecretion syndrome are mainly attributable to the small size of these lesions and the fact that they frequently escape direct radiologic depiction, although surgical interventions at the pituitary level frequently reveal an adenoma, the resection of which usually leads to a remission of the disease. The relatively low frequency of ACTH-dependent Cushing syndrome was an obstacle for compiling pertinent data on the diagnostic value of radiographs, thin-collimation computed tomography (CT), and magnetic resonance imaging (MR). To date, no such comparative study allowing statistical evaluation has been performed, to our knowledge. We therefore have reviewed the preoperative radiologic data of 141

Received January 24, 1992; revision requested April 9; final revision received October 6 and accepted October 14.

All authors: Neurochirurgische Klinik mit Poliklinik der Universität Erlangen-Nürnberg, 91054 Erlangen, Germany.

Address reprint requests to Dr. Michael Buchfelder, Neurochirurgische Klinik der Universität Erlangen-Nürnberg, Schwabachanlage 6, D-8520 Erlangen, Germany.

AJNR14:1183–1190, Sep/Oct 1993 0195-6108/93/1405-1183
© American Society of Neuroradiology

Fig. 1. Examples of different types of sella region CT findings in Cushing disease.

A, No evidence of abnormal structures.

B, Direct depiction of intrasellar microadenoma.

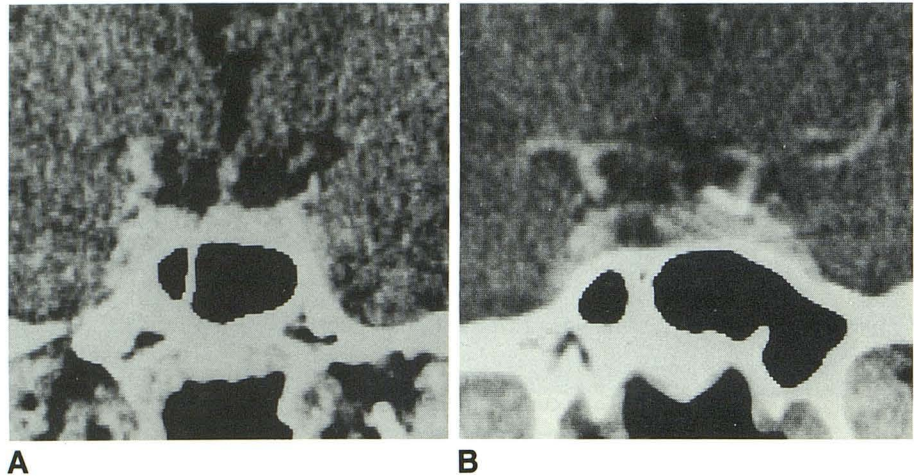


TABLE 1: Tumor size and CT findings (n = 125) in relation to treatment results after surgery

Tumor Size	Total	Remission		Persistent Disease	
		Lesion Seen at Surgery	Lesion Detected by CT	Lesion Seen at Surgery	Lesion Detected by CT
No tumor (n = 17)	125	81	44	44	15
Microadenomas	98	73	37	25	10
Up to 2 mm	8	7		1	
2-4 mm	32	23	6	9	2
4-6 mm	41	28	21	13	6
6-8 mm	12	10	6	2	2
8-10 mm	5	5	4		
Macroadenomas	10	7	7	3	3

^a Hemihypophysectomy.

^b False-positive imaging.

consecutive patients who underwent transsphenoidal surgery for Cushing disease in our department within an 8.5-year period up to March 31, 1991.

Patients and Methods

A consecutive series of surgically treated patients with ACTH-dependent Cushing disease were analyzed with respect to the radiologic findings of the sella turcica prior to transsphenoidal pituitary surgery. They underwent operations between December 1, 1982 and March 31, 1991. The patients were shown to have Cushing disease by dynamic endocrine testing as described previously (2). Routine endocrine investigation included low- and high-dose dexamethasone testing, corticotropin-releasing hormone stimulation tests, and assessment of anterior pituitary function after administration of luteinizing hormone-releasing hormone and thyrotropin-releasing hormone with determinations of all pituitary hormones. The initial preoperative interpretations of the imaging studies were correlated with the surgical findings and patient follow-up. The interpreters were blinded to the diagnosis and surgical findings. Two readers were used to interpret each study.

This series of patients included men and women, ranging from 23 to 66 years of age. They were divided into two groups: those with (n = 96) and those without (n = 45) remission from hypercortisolism after pituitary surgery.

One hundred twenty-five patients were studied by thin-collimation CT. The CT examinations were performed on Siemens (Erlangen, Germany) Somatom DR and DRH high-resolution scanners, respectively. Thin-collimation (2-mm) axial CT scans with sagittal and coronal computed reformations or direct coronal views, before and immediately after bolus injection of contrast medium, were obtained in all 125 cases.

Seventy-eight patients had extensive MR studies. The MR examinations were performed on a Siemens Magnetom 1.5-T superconducting magnet with a head coil. Multisection spin-echo pulse sequences were used. Sagittal and coronal T1-weighted images were acquired with a TR ranging from 300 to 700 milliseconds and a TE ranging from 15 to 40 milliseconds. Section thickness decreased from 4 mm initially in the early scans to 3 mm since 1987. A standard 256 × 256 acquisition matrix was used. Routinely, magnified views of the sella region were obtained. Paraxial slices parallel and through the pituitary stalk were made in all cases in order to detect the indirect sign of

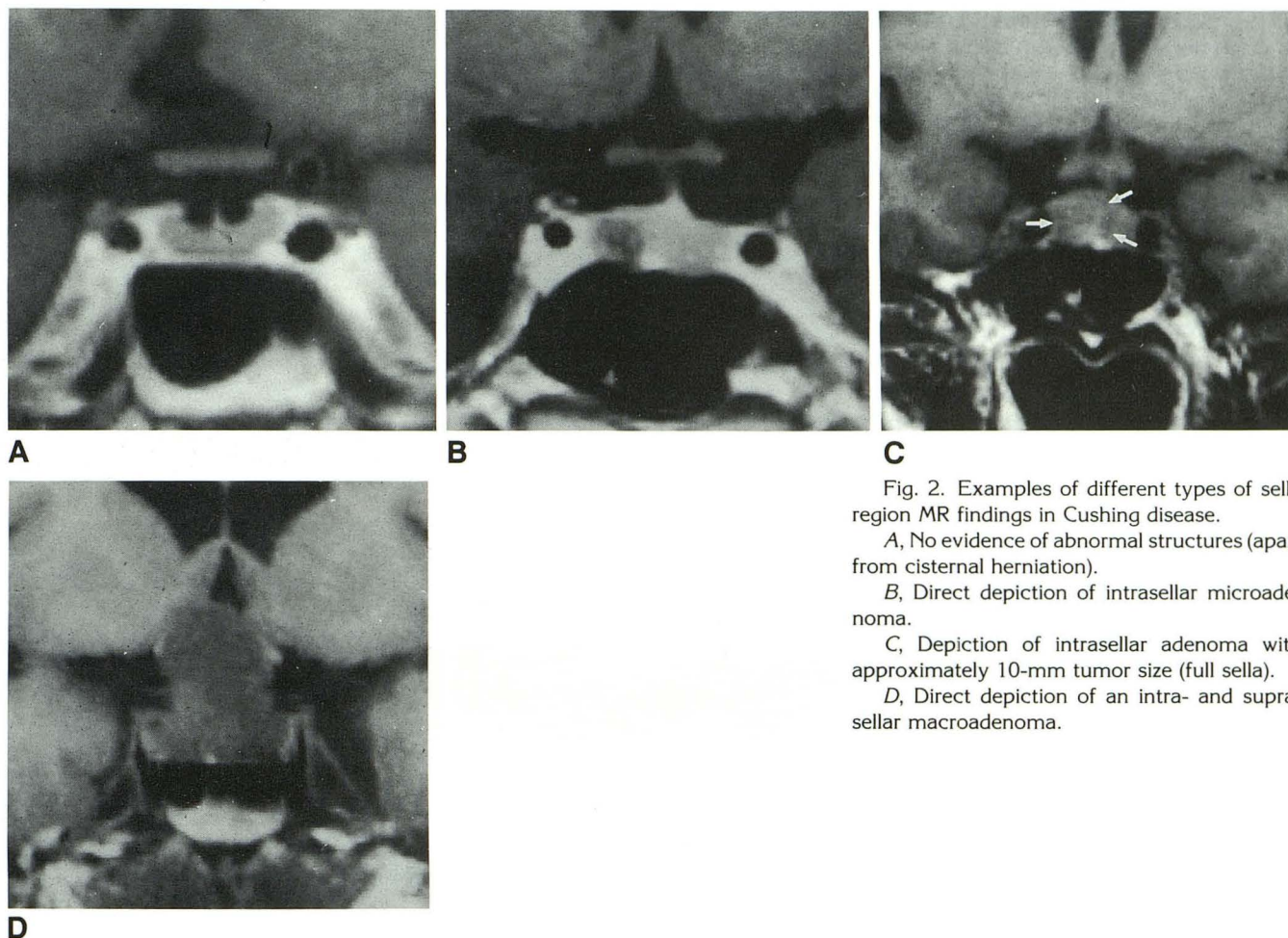


Fig. 2. Examples of different types of sella region MR findings in Cushing disease.

A, No evidence of abnormal structures (apart from cisternal herniation).

B, Direct depiction of intrasellar microadenoma.

C, Depiction of intrasellar adenoma with approximately 10-mm tumor size (full sella).

D, Direct depiction of an intra- and supra-sellar macroadenoma.

TABLE 2: Tumor size and MR findings (n = 78) in relation to treatment results after surgery

Tumor size	Total	Remission		Persistent Disease	
		Lesion Seen at Surgery	Lesion Detected by MR	Lesion Seen at Surgery	Lesion Detected by MR
No tumor (n = 16)	78	54	33	24	5
Microadenomas	52	41	24	11	4
Up to 2 mm	3	3			
2-4 mm	25	20	7	5	1
4-6 mm	19	14	13	5	2
6-8 mm	3	3	3		
8-10 mm	2	1	1	1	1
Macroadenomas	10	9	9	1	1

^a Hemihypophysectomy.

pituitary stalk shifting. Gadolinium-enhanced scans were additionally obtained in 11 of the 78 patients investigated. Enhanced scans were obtained immediately after gadolinium administration.

In microadenomas the CT and MR films were primarily evaluated with respect to the direct depiction of a typical intrasellar low density (CT) or low signal intensity region on the T1-weighted images (MR). Secondly, indirect signs of an intrasellar tumor were searched for, namely an

upward bulging of the gland, a lateral displacement of the pituitary stalk, and an asymmetric sellar floor. Additionally, in the patients assessed by MR an eccentric displacement of the hyperintense signal of the posterior pituitary and the disappearance of the hyperintense signal of blood flow in the vein of the carotid sulcus or in the medial cavernous sinus veins on gadolinium-enhanced scans were considered indirect evidence of intrasellar adenoma. Scans lacking direct or indirect signs of intrasellar adenoma were classified

Fig. 3. Influence of paramagnetic contrast medium (gadolinium-DTPA) on the direct depiction of intrasellar microadenomas in Cushing disease. An isointense, invisible microadenoma (A) becomes evident after administration of gadolinium DTPA (B).

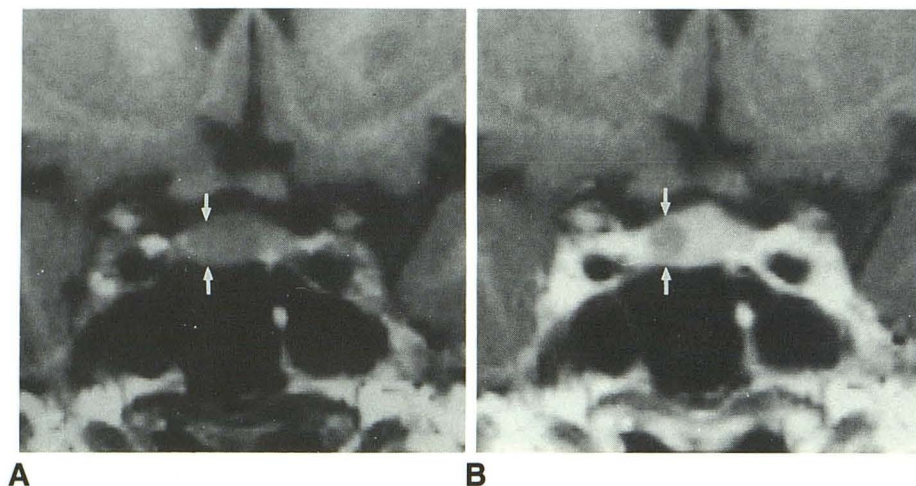
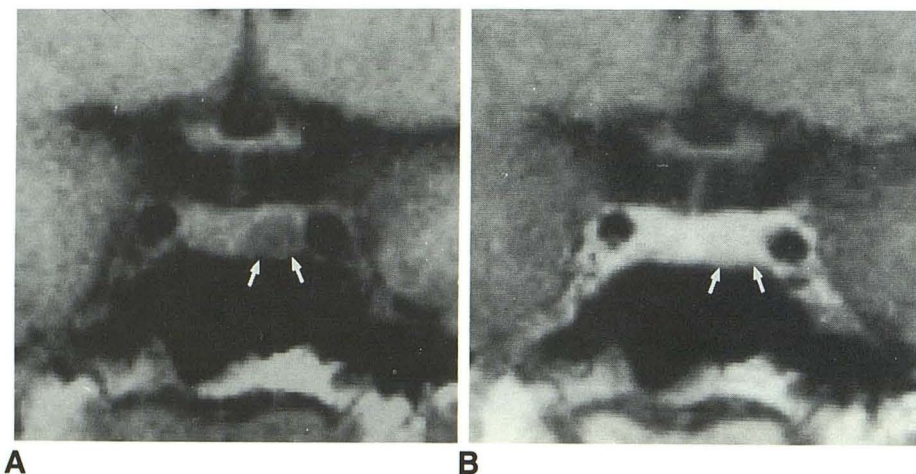


Fig. 4. Influence of paramagnetic contrast medium (gadolinium-DTPA) on the direct depiction of intrasellar microadenomas in Cushing disease. A clearly visible microadenoma (A) disappears after administration of gadolinium-DTPA (B).



as normal. Furthermore, the scans were reviewed for the presence or absence of intrasellar herniation of the subarachnoid space (partially empty sella). Of the total of 141 patients, only 62 were assessed by both CT and MR.

The radiologic findings were related to the intraoperative findings with respect to the total size of the tumor resected and its location. The outcome of surgery was classified according to the result of low-dose dexamethasone testing 3 months after operation. The finding of cortisol levels suppressible to less than $2 \mu\text{g/dL}$ was regarded as biochemical proof of remission from the disease. The determination of the specificity of the respective neuroradiologic investigations was related to the group of 96 patients who were found to have a remission from hypercortisolism after surgery. For the correlation of neuroradiologic and surgical findings, diameter, extension of the adenoma, and tumor configuration were quoted. Identical or very similar findings were rated as "good." If the tumor was detected and located only in part by neuroimaging methods, the correlation was specified as "fair." A rating of "poor" denoted a false location of the tumor by neuroimaging or the inability of the neuroradiologist to correctly locate at least a part of the tumor.

Selective adenomectomy was performed whenever a discrete pituitary adenoma was identified during pituitary microsurgery.

Results

Thin Collimation CT

Of the 125 patients assessed by thin collimation CT scanning, 98 patients had microadenomas, and 10 had macroadenomas. Apart from macroadenomas, two different types of CT presentation were distinguished (Fig. 1). In 17 cases, no tumor was found during microsurgery of the pituitary gland. All 10 macroadenomas were directly depicted. Invasion of structures surrounding the sella was encountered in four patients during surgery but preoperatively recognized by CT findings in only one case. In two of the 17 patients in whom no tumor was found during surgery, the CT scans had suggested the presence of a circumscribed intrasellar lesion by depicting

TABLE 3: Detectability by CT and MR imaging of surgically verified pituitary microadenomas in Cushing disease, in relation to tumor size as estimated during surgery

Tumor Size (mm)	MR Detectability (%)	CT Detectability (%)
1		
2	33.3	14.3
3	40	31.6
4	80	53.8
5	90	60.8
6	88.8	83.3
7	100	60
8	100	85.7
9	100	100
10	100	100
Overall	71.1	59.1

a low-density region in two cases. However, the other 15 scans were reported to be normal. One of the patients had a remission from hypercortisolism following a hemihypophysectomy according to the ACTH gradient obtained during bilateral simultaneous inferior petrosal sinus blood sampling. Of the 98 microadenomas found by the surgeon, only 47 were directly depicted by a clearly circumscribed low-density region. The relation between tumor diameter as found during pituitary surgery and the detection rate of indirect and direct signs of an intrasellar adenoma is summarized in Table 1.

MR

Of 78 patients assessed by MR, 52 had microadenomas, and 10 had macroadenomas. In 16 patients, no tumors were found during pituitary microsurgery. Again, four different types of MR presentation were distinguished (Fig. 2). All 10 macroadenomas were directly depicted. Invasion of structures surrounding the sella turcica was encountered in three patients during surgery but was preoperatively recognized by the MR findings in only two cases. There was no case of a false-positive demonstration of a discrete hypointense intrasellar lesion among the 16 cases in whom sella exploration did not reveal a pituitary microadenoma. Three of these patients had a remission from hypercortisolism following a hemihypophysectomy according to the ACTH gradient obtained during bilateral simultaneous inferior petrosal sinus sampling. The relation of tumor diameter as found during pituitary surgery and the detection rate of indirect and direct signs of an intrasellar adenoma are summarized in Table 2.

In addition to the unenhanced MR scans, gadolinium-DTPA was used as a paramagnetic contrast medium in 11 patients. The paramagnetic agent improved the quality of preoperative scans in only two of eight patients later shown during surgery to harbor a pituitary microadenoma (Fig. 3). The microadenomas measured 5 to 6 mm and 8 to 9 mm, respectively. In both cases the adenomas were isointense on nonenhanced MR scans and became visible as a nonenhancing intrasellar zone on gadolinium-enhanced scans. However, in both of these cases obvious indirect signs signaled the presence of an intrasellar adenoma even on nonenhanced scans. In two other cases of microadenomas with diameters of 4 and 5 mm, respectively, the tumor was clearly detectable as an intrasellar hypointense region on nonenhanced scans. After administration of gadolinium the tumors enhanced in a way similar to the adjacent normal pituitary gland and thus became less visible (Fig. 4). In the remaining four adenomas the adenomas were clearly visible on both nonenhanced and enhanced scans.

CT versus MR

A total of 62 patients had both CT and MR prior to surgery. Of these, 41 had microadenomas; eight had macroadenomas. In 13 of these cases, no tumor was found during microsurgical sella exploration. In the 8 cases with macroadenomas, CT and MR were equally effective in depicting the size and extension of the tumors. However, in the three tumors with parasellar development, MR provided a better delineation of the adenomas and the connection of intra- and parasellar tumor parts.

Of the 41 cases with microadenomas, 13 were directly depicted by CT, and 20 were directly depicted by MR. In only one instance was a 6-mm microadenoma directly depicted by CT but not shown by MR. On the other hand, in six cases MR directly depicted an intrasellar adenoma, although the CT scans had revealed only indirect signs of an intrasellar lesion. In an additional five cases there was neither direct nor indirect detection of a tumor on CT, but there was depiction of a hypointense signal region corresponding to a microadenoma on MR. Thus, in 11 out of 41 cases with microadenomas the MR findings were clearly superior. In 29 cases the morphologic information about the tumor provided by CT and MR were equivalent. CT detected abnormalities in 59.1% of those patients who were later found

TABLE 4: Correlation of CT and MR images with the operative findings in surgically cured patients

Correlation	Number of Cases				%			
	CT (n = 74)		MR (n = 45)		CT (n = 74)		MR (n = 45)	
	No Tumor Found (n = 1)	Tumor Confirmed (n = 73)	No Tumor Found (n = 4)	Tumor Confirmed (n = 41)	No Tumor Found (n = 1)	Tumor Confirmed (n = 73)	No Tumor Found (n = 4)	Tumor Confirmed (n = 41)
Good	1/1	31/73	4/4	21/41	100	42	100	52
Fair		15/73		10/41		21		24
Poor		27/73		10/41		37		24

to harbor microadenomas; MR was considered abnormal in 71.1% of these lesions. The detectability of microadenomas by CT and MR in correlation with the intraoperatively estimated size of the tumors are summarized in Table 3.

The results of pituitary imaging clearly were a prognostic factor for the outcome after pituitary surgery. When a distinct microadenoma was depicted by CT, 37 of 47 patients (78.7%) had remission after surgery. However, if the scan was negative, only 28 of 58 patients (51.7%) remitted. A hypointense, well-demarcated intrasellar lesion on MR similarly was a favorable prognostic indicator, because in 24 of 28 patients (85.7%) with this finding the hypercortisolism was corrected by pituitary surgery. Correspondingly, 17 of 31 patients with negative MR scans had persistent disease after the operation. In 19 of the 141 patients no adenoma was found. Four out of eight patients in whom no discrete microadenoma was found during sella exploration, and who had a significant ACTH gradient when inferior petrosal sinus sampling was performed, had a remission following respective hemihypophysectomy.

Neuroradiologic vs Surgical Topography

In 16 cases in which no tumors were found, the MR findings were never false positive. In contrast, the CT scan falsely suggested adenomas that could not be confirmed by both surgeon and pathologist in two of the 17 cases. The correlation between CT and MR findings, respectively, and the surgical topography is summarized in Table 4. There was an excellent correlation in the detection of intrasellar cysternal herniation, which was found in 31 out of the total 141 cases.

Discussion

Because hypercortisolism may be attributable to a variety of different causes, and because it may be difficult even after extensive dynamic

functional testing to locate precisely the source of cortisol hypersecretion (6, 7), the neuroradiologist is frequently expected to contribute to the differential diagnosis of Cushing syndrome. However, the vast majority of pituitary adenomas associated with ACTH-dependent Cushing syndrome (Cushing disease) are small lesions. With the development of thin-collimation CT and MR neuroradiology of pituitary lesions, sella tomography is no longer used and is today considered to have only historical relevance.

The sensitivity of thin-collimation CT scans to detect microadenomas of the pituitary gland in Cushing disease directly was reported to range from 17% (8) to 58.3% (9). Indirect signs of an adenoma, such as upward bulging of the gland's upper surface or pituitary stalk deviation, were more frequently found (8–10). There was some debate as to whether direct coronal scanning with bolus contrast application could improve the diagnostic accuracy (11). By using a specialized software system, and by carefully controlling the CT procedures, paying attention to the individual patient's requirements, Bonneville et al (12) have obtained results comparable to MR findings even when applied to patients with pituitary microadenomas. However, Marcovitz et al (9), who have used direct coronal scans, report microadenomas found during pituitary microsurgery in 10 out of 15 patients with negative scans. Furthermore, the detection of radiologic abnormalities does not necessarily imply that the images depicted represent the morphologic reality. Teasdale et al (13) have correlated the findings of reformatted thin-collimation CT images with the operative findings in 14 patients who underwent transsphenoidal surgery for Cushing disease. In 5 of the cases CT gave false indications of the anatomic locations of the ACTH-secreting adenomas. Only one of three patients in whom no distinct microadenoma was found during surgery had a small pituitary gland without radiologic abnormalities on CT. In our series, the smallest microadenoma directly

visualized by reformatted CT images in a patient whose hypercortisolism was corrected by resection of the tumor had an estimated diameter of 3 mm. Bone-hardening artifacts within the sella may be mistaken for pituitary microadenomas in coronal or sagittal reformatted images. In these, the streak artifacts may appear as rounded hypodense lesions. These hypodense regions may not be recognized as artifacts in reformatted images, which is their major disadvantage. Although fat deposition in the cavernous sinus (14) is more frequently noted in Cushing disease than in other pituitary hypersecretion syndromes, it is not a pathognomonic sign.

The sensitivity of MR in directly detecting ACTH-secreting microadenomas was reported to range from 44.9% (15) to 71% (16). Indirect evidence of a microadenoma by some kind of pituitary stalk deviation was found in 59% of the patients (17). Although the use of gadolinium was believed by some authors to increase the sensitivity of direct detection (15, 18), we have seen two cases in which microadenomas became invisible after contrast enhancement. Generally, the capability of detecting small microadenomas seems to be slightly increased by MR if compared with CT. The smallest microadenoma directly depicted by MR in a patient who had a correction of hypercortisolism after pituitary microsurgery had an estimated diameter of 3 mm.

Although the association of pituitary microadenomas with Cushing disease and intrasellar cystic herniation has occasionally been reported (17, 19), little attention has been paid to it in the literature. We have found some kind of intrasellar arachnoid in 22% of our patients. Among these, there was only one patient in whom enlargement of the sella turcica could not be radiologically attributed to a distinct microadenoma. It is obvious that the chance of detecting and correctly localizing the adenoma intraoperatively increases dramatically with its size.

In cases with the biochemical diagnosis of pituitary-dependent Cushing disease in which there is no microadenoma visualized by sophisticated imaging techniques, there is a smaller chance that a microadenoma is found during pituitary microsurgery. In addition, there is a smaller chance of remission following pituitary microsurgery. We therefore would recommend that this subgroup of patients should be submitted for simultaneous petrosal sinus sampling to confirm the diagnosis and to increase the chance of surgical cure by providing a basis for partial

hypophysectomy according to the ACTH gradient (20, 21).

Our study was performed on a highly selected group of patients, who were found to have the typical biochemical characteristics of Cushing disease during dynamic endocrine testing (2, 7). Therefore, it does not allow us to draw conclusions on radiologic findings of patients who suffer from hypercortisolism and who have neither hypothalamic nor pituitary disease. Nevertheless, the differential diagnosis of the syndrome is still predominantly based on the findings of classical biochemical testing. Neuroradiologic assessment of the sellar content provides a visualization of a distinct microadenoma in only 40% to 50% of the patients found on the basis of dynamic endocrine testing to have Cushing disease, in whom hypercortisolism was corrected by resection of a pituitary adenoma even when recent imaging technology is used.

References

1. Cushing H. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). *Bull Johns Hopkins Hosp* 1932;50:137-195
2. Fahlbusch R, Buchfelder M, Müller OA. Transsphenoidal surgery for Cushing's disease. *J R Soc Med* 1986;79:262-269
3. Laws ER. Cushing's disease: neurosurgical viewpoints. In: van Heerden JA, ed. *Common problems in endocrine surgery*. Chicago: Year Book Medical, 1989:18-22
4. Mampalam TJ, Tyrrell JB, Wilson CB. Transsphenoidal microsurgery for Cushing's disease: a report of 216 cases. *Ann Intern Med* 1988;109:487-493
5. Nakane T, Kuwayama A, Watanabe M, et al. Long term results of transsphenoidal adenomectomy in patients with Cushing's disease. *Neurosurgery* 1987;21:218-222
6. Trainer PJ, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome. *Clin Endocrinol (Oxf)* 1991;34:317-330
7. Kaye TB, Crapo L. The Cushing syndrome: an update of diagnostic tests. *Ann Intern Med* 1990;112:434-444
8. Saris SC, Patronas NJ, Doppman JL, et al. Cushing syndrome: pituitary CT scanning. *Radiology* 1987;162:775-777
9. Marcovitz S, Wee R, Chan J, Hardy J. The diagnostic accuracy of preoperative CT scanning in the evaluation of pituitary ACTH-secreting adenomas. *AJNR: Am J Neuroradiol* 1987;8:641-644
10. Pojunaas KW, Daniels DL, Williams AL, Thorsen MK, Haughton VM. Pituitary and adrenal CT of Cushing syndrome. *AJNR: Am J Neuroradiol* 1986;7:271-274
11. Bonneville JF, Cattin F, Moussa-Bacha K, Portha C. Dynamic computed tomography of the pituitary gland. The "Tuft Sign." *Radiology* 1983;149:145-148
12. Bonneville JF, Cattin F, Dietemann JL. ACTH-secreting pituitary adenomas. In: *Computed tomography of the pituitary gland*. Berlin: Springer, 1986:137-144
13. Teasdale E, Teasdale G, Mohsen F, Macpherson P. High-resolution computed tomography in pituitary microadenoma: Is seeing believing? *Clin Radiol* 1986;37:227-232
14. Bachow TB, Hesselink JR, Aaron JO, Davis KR, Taveras JM. Fat deposition in the cavernous sinus in Cushing disease. *Radiology* 1984;153:135-136

15. Dwyer AJ, Frank JA, Doppman JL, et al. Pituitary adenomas in patients with Cushing's disease: initial experience with Gd-DTPA enhanced MR imaging. *Radiology* 1987;163:421-426
16. Peck WW, Dillon WP, Norman D, Newton TH, Wilson CB. High-Resolution MR imaging of microadenomas at 1.5 T: experience with Cushing disease. *AJNR: Am J Neuroradiol* 1988;9:1085-1091
17. Johnson ZS, Phillips J, Devlin J, O'Donnell J. Intracellar subarachnoid space in Cushing's disease. *Ir Med J* 1983;76:358
18. Doppman JL, Frank JA, Dwyer AJ, et al. Gadolinium DTPA enhanced MR imaging of ACTH-secreting microadenomas of the pituitary gland. *J Comp Assist Tomogr* 1988;12:728-735
19. Ganguly A, Stanchfield JB, Roberts TS, West CD, Tyler FH. Cushing's syndrome in a patient with an empty sella turcica and a microadenoma of the adenohypophysis. *Am J Med* 1976;60:306-309
20. Miller DL, Doppman JL, Nieman LN, et al. Petrosal sinus sampling: discordant lateralization of ACTH-secreting pituitary microadenomas before and after stimulation with corticotropin-releasing-hormone. *Radiology* 1990;176:429-431
21. Oldfield EH, Chrousos GP, Schulte HM, et al. Preoperative lateralization of ACTH-secreting pituitary microadenomas by bilateral and simultaneous inferior petrosal sinus sampling. *N Engl J Med* 1985;312:100-103