High-dose dexamethasone suppression test is inferior to pituitary dynamic enhanced MRI in the differential diagnosis of ACTH-dependent Cushing’s syndrome

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Abstract
Purpose The differential diagnosis of adrenocorticotropic hormone (ACTH)-dependent Cushing’s syndrome remains a challenge in clinical practice. The present study was aimed at assessing the diagnostic performance of pituitary dynamic contrast-enhanced magnetic resonance imaging (dMRI), high-dose dexamethasone suppression test (HDDST), and a combination of both tests for patients with ACTH-dependent Cushing’s syndrome.
Methods A total of 119 consecutive patients with ACTH-dependent Cushing’s syndrome confirmed surgically were enrolled: 101 with proven Cushing’s disease and 18 with proven ectopic ACTH syndrome. All patients underwent pituitary dMRI and HDDST. The sensitivity and specificity of pituitary dMRI, HDDST, and a combination of both tests were determined.
Results The sensitivity and specificity of pituitary dMRI for diagnosing Cushing’s disease were 80.2 and 83.3%, respectively, with a positive predictive value of 96.4%. The sensitivity and specificity of HDDST were 70.3 and 77.8%, respectively, with positive predictive value of 94.7%. A combination of both tests showed that the combined criteria of more than 50% suppression of serum cortisol on HDDST and a positive pituitary dMRI finding yielded a high specificity of 94.4 and sensitivity of 59.4%. The combined criteria of more than 68% suppression on HDDST and/or a positive pituitary dMRI finding yielded a sensitivity of 86.1% and specificity of 83.3%.
Conclusions Pituitary dMRI was superior to HDDST in the differential diagnosis of ACTH-dependent Cushing’s syndrome. HDDST is recommended in combination with pituitary dMRI to establish a diagnosis process because of the significantly increased specificity with the combination.

Keywords Cushing’s syndrome · Dynamic contrast-enhanced magnetic resonance imaging · HDDST

Abbreviations
CS Cushing’s syndrome
ACTH adrenocorticotropic hormone
CD Cushing’s disease
EAS ectopic ACTH syndrome
dMRI dynamic contrast-enhanced magnetic resonance imaging
HDDST high-dose dexamethasone suppression test
BIPSS bilateral inferior petrosal sinus sampling
CRH corticotrophin-releasing hormone
PET positron emission tomography.

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**Introduction**

Cushing’s syndrome (CS) is a clinical condition wherein the adrenal gland secretes excessive glucocorticoids. It can be divided into adrenocorticotropic hormone (ACTH)-dependent CS and ACTH-independent CS. ACTH-dependent CS is caused by tumors that produce ACTH. The two main types of ACTH-dependent CS are Cushing’s disease (CD) caused by pituitary adenomas and ectopic ACTH syndrome (EAS) resulting from ACTH-secreting tumors outside the pituitary, such as thymic and bronchial carcinoid tumors, and medullary thyroid carcinoma.

The diagnosis of ACTH-dependent CS is challenging in clinical practice, with the core problem being difficulty in distinguishing between ACTH-producing pituitary adenomas and extra-pituitary sources of ACTH secretion. Bilateral inferior petrosal sinus sampling (BIPSS) is an accurate method with high sensitivity and specificity to distinguish CD from EAS [1]. However, this technology is expensive and invasive, and non-invasive examinations are typically preferred in clinical practice.

The three main non-invasive tests are high-dose dexamethasone suppression test (HDDST), corticotrophin-releasing hormone (CRH) test, and desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) test [2]. The CRH test is the most reliable non-invasive method [3]. The DDAVP test could be an alternative to the CRH test but is not as effective as the CRH test [2, 4]. However, the availability of these two tests is limited in many areas and countries because of the lack of commercial accessibility to desmopressin and CRH. Over the years, the HDDST has been largely used to distinguish CD from EAS, where CRH test is not available. A positive test response is a decrease of cortisol to at least or more than 50% of baseline values. The HDDST result is typically positive in patients with CD and negative in patients with EAS. However, some patients with severe CD, particularly those with large pituitary tumors and high cortisol levels, may have an absent response, while almost 10% of patients with EAS have a positive response [5].

Magnetic resonance imaging (MRI) has been the gold standard imaging modality used to study the pituitary gland. However, approximately 50% of patients have false-negative results on conventional pituitary MRI [6], which limits its value in the diagnosis of CD. Dynamic contrast-enhanced MRI (dMRI), a method of dynamically acquiring T1-weighted MRI scans after intravenous injection of contrast agents, can provide more information about pituitary adenomas than conventional MRI [7]—this could potentially improve the sensitivity of pituitary tumor detection but may reduce the specificity of detection [8]. The aim of the present study was to assess the diagnostic performance of pituitary dMRI, HDDST, and a combination of both tests in a consecutive series of patients with ACTH-dependent CS.

**Methods**

**Participants**

In this retrospective study, we enrolled a consecutive series of patients with ACTH-dependent CS admitted to our hospital between 2008 and 2020, including patients diagnosed with CD and those diagnosed with EAS. Clinical, laboratory, radiological, pathological, treatment, and outcome data were obtained from the hospital records of all patients. Patients who did not undergo pituitary dMRI or the HDDST or received any drug known to affect the hypothalamic–pituitary–adrenal axis were excluded from the study. CS was diagnosed based on the criteria of the Endocrine Society Clinical Practice Guideline [9]. In all cases, the diagnosis was confirmed pathologically or based on the clinical remission status postoperatively. Written informed consent was obtained from all enrolled patients.

**HDDST**

Blood samples were collected at 8.00 AM, and plasma cortisol levels were measured and recorded as baseline values before the test. Subsequently, 2 mg of dexamethasone was administered orally every 6 h for two days, and plasma cortisol levels were measured at 8.00 AM the next morning. A suppression >50% in plasma cortisol levels from that at baseline was regarded as a positive result and was considered to be consistent with the diagnosis of CD.

**Imaging**

Pituitary dMRI was performed using a 3.0 T MRI scanner. Conventional T1-weighted and T2-weighted images were initially analyzed. A pituitary adenoma was considered when a focal change in signal occurred on any of the two sequences, as previously described [10]. On dMRI, a pituitary adenoma shows a lack of or a temporary delay in enhancement relative to the normal pituitary gland [10]. Lesions measuring <3 mm were considered indeterminate. Indirect signs, such as upward bulging of the pituitary gland or deviation of the infundibulum, were not considered diagnostic. Two experienced radiologists independently interpreted the images. They were informed of patients’ clinical information but were blinded to their surgical and pathological results. In case of a disagreement, consensus was aimed at through discussions. The radiological interpretations of pituitary dMRI were classified as positive,
indeterminate, or negative. In case of indeterminate results, the pituitary dMRI finding was considered negative.

**Laboratory assays**

Serum cortisol levels were measured using a chemiluminescent enzyme immunoassay. Plasma ACTH levels were measured using an immunoradiometric assay.

**Treatment and pathology**

Transsphenoidal surgery was performed in patients diagnosed with CD. Resection of ectopic ACTH-secreting tumors was performed in patients with EAS. The diagnosis was confirmed either based on positive ACTH staining on immunohistochemical analysis of the tumor or based on the clinical remission status postoperatively. Clinical remission refers to a decrease in serum cortisol levels to the normal range or lower than the normal range. The criteria for CD remission were as follows: (1) morning (8.00 AM) serum cortisol levels <5 µg/dL within seven days of selective tumor resection [11] and (2) achieving hypocortisolism (8.00 AM serum cortisol level <5 µg/dL) or eu cortisolism (8.00 AM serum cortisol level ≥5 µg/dL) and after the 1 mg overnight dexamethasone suppression test, serum cortisol level ≤1.8 µg/dL) at the follow-up visit (up to 6 months) [12, 13].

**Statistical analysis**

Continuous variables are expressed as mean ± SD, median, and interquartile range. The sensitivity, specificity, accuracy, false-positive ratio, false-negative ratio, positive predictive value, and negative predictive value of dMRI, HDDST, and a combination of both tests were calculated by comparing the results of each diagnostic procedure with those of the gold standard. The gold standard was positive pathological examination finding or clinical remission status postoperatively. A receiver operating characteristic (ROC) curve was also used to assess the value of dMRI, HDDST, and a combination of both tests for diagnosing CD. The area under the curve (AUC) was calculated, and the best cut-off values were defined. The point on the ROC curve, offering the highest specificity and sensitivity, provides the best cutoff value. Statistical analysis was performed using SPSS 24.0 software. P < 0.05 was considered to be statistically significant.

**Results**

**Demographic and clinical profile**

The study included 119 patients with ACTH-dependent CS, including 101 (84.9%) with CD and 18 (15.1%) with EAS. Demographic data showed that of the 119 patients with CS, 27 (22.7%) were men and 92 (77.3%) were women. The age range of the patients was 13–67 years, and the average age was 38.2 ± 12.5 years. The median midnight (23:00) plasma cortisol level was 23.7 (18.0, 32.7) µg/dL, and the median ACTH level was 24.3 (13.8, 40.8) pmol/L (ACTH norma range 1.6–13.9 pmol/L). All patients underwent HDDST and pituitary dMRI.

**Pituitary dMRI in the differential diagnosis of ACTH-dependent CS**

As shown in Fig. 1, 84 of 119 patients had definite positive findings on pituitary dMRI, of whom 16 had macro adenomas and 68 had microadenomas. Two of the 84 patients were definitively diagnosed with EAS. One patient underwent transsphenoidal surgery and had no clinical remission after surgery but was found to have EAS on positron emission tomography-computed tomography at a subsequent follow-up. Thus, in three of 84 dMRI-positive patients, an ectopic source of ACTH was found. The remaining 81 patients underwent transsphenoidal surgery. Among them, 73 were pathologically confirmed to have ACTH-positive pituitary adenomas; the remaining eight had pituitary tumors, but the histological results showed negative ACTH staining. These eight patients were diagnosed with CD based on the clinical remission status postoperatively.

Fourteen patients had indeterminate findings, and 21 patients had negative findings on pituitary dMRI; these 35 patients were classified as having negative findings. Among them, 13 patients were definitively diagnosed with EAS and thus did not undergo transsphenoidal surgery. The remaining 22 patients were referred for transsphenoidal surgery based on HDDST or IPSS results. Two of these 22 patients were not cured surgically and were found to have EAS at a subsequent follow-up. For the remaining 20 patients (12 with negative dMRI and eight with indeterminate dMRI findings), a pituitary source of ACTH was proven. Seventeen of these 20 patients were pathologically confirmed to have pituitary ACTH tumors. In the other three patients, though no tumor was found, remission after surgery proved the presence of a pituitary source of ACTH (Fig. 1, Table 1).

The sensitivity and specificity of pituitary dMRI to detect a pituitary source of ACTH were 80.2 and 83.3%, respectively, with an accuracy of 80.7%. The positive and negative predictive values were 96.4 and 42.9%, respectively. The false-negative and false-positive rates were 19.8 and 16.7%, respectively. Table 2 shows the diagnostic performance of pituitary dMRI for the diagnosis of CD.

Compared with dMRI, conventional T1- and T2-weighted imaging reported an adenoma in 60 of 101
patients with CD. Two out of 18 cases of EAS had positive findings on conventional T1- and T2-weighted imaging. Thus, the sensitivity of conventional MRI was 59.4%, whereas the specificity was 88.9%, and the accuracy was 63.9%.

**HDDST in the differential diagnosis of ACTH-dependent CS**

A positive HDDST result was observed in 71 of 101 cases of CD and four of 18 cases of EAS (Table 1). Here, a positive result referred to suppression of the plasma cortisol level after dexamethasone administration to less than half of the baseline level.

The sensitivity of HDDST for CD diagnosis was 70.3%, specificity was 77.8%, and accuracy was 71.4%. The negative and positive predictive values were 31.8 and 94.7%, respectively, and the false-negative and false-positive rates were 29.7 and 22.2%, respectively (Table 2).

Among patients with pituitary microadenomas, 49 (75.4%) of the 65 patients with CD and one of the three patients with EAS had a positive HDDST result (Fig. 1). Therefore, in patients with pituitary microadenomas, the sensitivity of HDDST was 75.4%, specificity was 66.7%, and accuracy was 75%. The positive predictive value was 96.1%. Among patients with pituitary macroadenomas, only 11 (68.7%) of the 16 patients with CD had a positive HDDST result. No EAS cases were reported among patients with pituitary macroadenomas; therefore, evaluating the specificity and sensitivity of HDDST was not possible in cases of pituitary macroadenomas.

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**Table 1** Diagnostic confirmation and classification of patients evaluated with pituitary dMRI and HDDST

| Diagnosis                        | CD  | EAS |
|----------------------------------|-----|-----|
| Pituitary dMRI                   |     |     |
| Positive                         | 81  | 3   | 80.7|
| Negative                         | 20  | 15  |
| HDDST                            |     |     |
| Suppression (positive)           | 71  | 4   | 71.4|
| No suppression (negative)        | 30  | 14  |
| Combined pituitary dMRI and HDDST|     |     |
| Both positive                    | 60  | 1   | 64.7|
| At least one negative            | 41  | 17  |
| Combined pituitary dMRI and HDDST|     |     |
| At least one positive            | 92  | 6   | 87.4|
| Both negative                    | 9   | 12  |

Diagnosis: based on pathological examination or clinical remission
Both positive: positive findings in pituitary dMRI and cortisol levels suppressed by HDDST

*CD* Cushing’s disease, *EAS* ectopic adrenocorticotropic hormone syndrome, *dMRI* dynamic enhanced MRI, *HDDST* high-dose dexamethasone suppression tests
Table 2 Diagnostic performance of pituitary dMRI and HDDST in detecting a pituitary source of ACTH

| Test                          | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | False negative rate (%) | False positive rate (%) |
|-------------------------------|----------------|----------------|-----------------------------|------------------------------|------------------------|------------------------|
| Pituitary dMRI                | 80.2           | 83.3           | 96.4                        | 42.9                         | 19.8                   | 16.7                   |
| HDDST                         | 70.3           | 77.8           | 94.7                        | 31.8                         | 29.7                   | 22.2                   |
| Combined pituitary dMRI and   | 59.4           | 94.4           | 98.4                        | 29.3                         | 40.6                   | 5.6                    |
| HDDST (both positive)         |                |                |                             |                              |                        |                        |
| Combined pituitary dMRI and   | 91.1           | 66.7           | 93.9                        | 57.1                         | 8.9                    | 33.3                   |
| HDDST (either positive)       |                |                |                             |                              |                        |                        |

**Combined pituitary dMRI and HDDST in the differential diagnosis of ACTH-dependent CS**

Sixty-one patients had definite positive findings on pituitary dMRI and positive HDDST results, of whom 60 had CD and 1 had EAS. The remaining 58 patients had either negative findings on pituitary dMRI or negative HDDST results, of whom 41 had CD and 17 had EAS (Table 1). Thus, the combined test had a sensitivity of 59.4%, specificity of 94.4%, and accuracy of 64.7% for the diagnosis of CD. The negative and positive predictive values were 29.3 and 98.4%, respectively, and the false-negative and false-positive rates were 40.6 and 5.6%, respectively (Table 2).

Ninety-eight patients had either positive findings on pituitary dMRI or positive HDDST results, of whom 92 had CD and six had EAS. The remaining 21 patients had negative findings on pituitary dMRI and negative HDDST results, of whom nine had CD and 12 had EAS (Table 1). Thus, the combined test had a sensitivity of 91.1%, specificity of 66.7%, and accuracy of 87.4% for the diagnosis of CD. The negative and positive predictive values were 57.1 and 93.9%, respectively, and the false-negative and false-positive rates were 8.9 and 33.3%, respectively (Table 2).

**ROC analyses of HDDST, dMRI, and HDDST + dMRI**

Though a 50% suppression of serum cortisol levels after HDDST is a widely used cut-off, to avoid bias from predetermined criteria, ROCs were prepared for HDDST and dMRI for the differential diagnosis of CD from EAS. We then calculated the ROC-based cut-off for the HDDST. As shown in Fig. 2, the AUC of the HDDST was 0.809 [95% confidence interval (CI), 0.714–0.903; P < 0.001]. The optimal cut-off value was greater than 42.5% of suppression; it had a sensitivity of 76.2% and a specificity of 77.8% for CD diagnosis. The AUC of dMRI was 0.818 (95% CI, 0.709–0.927; P < 0.001), showing that dMRI was marginally superior to HDDST alone in the differential diagnosis of ACTH-dependent CS.

To further determine whether the combination of HDDST and dMRI achieved a higher diagnostic accuracy, we constructed an ROC curve for HDDST + dMRI (Fig. 2).

The AUC of HDDST + dMRI was 0.875 (95% CI, 0.779–0.971; P < 0.001). The optimal cut-off value was greater than 68% of suppression of serum cortisol after HDDST and/or a positive finding on pituitary dMRI, which had a sensitivity of 86.1% and a specificity of 83.3% for CD diagnosis. Thus, a higher diagnostic accuracy was achieved with the combination of HDDST and dMRI.

**Discussion**

Differentiation between CD and EAS remains one of the most challenging issues for clinical endocrinologists. In the current study, we investigated non-invasive tests (pituitary dMRI and HDDST) for the differential diagnosis of ACTH-dependent CS. We found that both the specificity and sensitivity of pituitary dMRI were higher than that of the HDDST. The combination of HDDST and pituitary dMRI provided a higher diagnostic accuracy than HDDST or dMRI alone in the differential diagnosis of ACTH-dependent CS.

MRI is the best imaging tool for the detection of pituitary tumors. However, the low sensitivity of conventional pituitary MRI limits its value in the differential diagnosis of CS. The sensitivity of conventional pituitary MRI for detecting ACTH-secreting pituitary adenomas is highly variable in the literature, and approximately 30–50% of pituitary adenomas are generally believed to be incorrectly identified [14–16]. With advancements in MRI technology, the detection rate of pituitary adenomas has improved significantly. Pituitary dMRI can obtain repeated images within a few seconds after the injection of a contrast agent, providing more information about pituitary adenomas than the conventional MRI. Though pituitary dMRI improves the sensitivity of pituitary adenoma detection, it is usually considered to be associated with an increased false-positive rate [17]. The sensitivity and false-negative rate of pituitary dMRI in our study were 80.2 and 19.8%, respectively. These findings indicate that in less than 20% of patients with CD, pituitary dMRI failed to detect the presence of pituitary adenoma. The false-negative results can be partly attributed to the small size of the pituitary adenoma or
similarities in the signal and enhancement features of the lesions and the normal pituitary. Notably, in three cases with false-negative dMRI findings, the presence of ACTH-secreting adenoma could not be confirmed surgically or pathologically. For these patients, the final diagnosis of CD became clear because hypercortisolemia was completely cured after surgery. This phenomenon occurs because the histological examination result of the pituitary in patients with CD is often negative owing to the small size of ACTH adenomas [6, 18, 19]. The specificity and false-positive rate of pituitary dMRI in our study were 83.3 and 16.7%, respectively. The specificity of pituitary dMRI ranges from 62 to 84%, as previously reported [8, 17, 20]. False positives mainly result from the incidence of asymptomatic pituitary microadenomas or technical artifacts. This suggests that the pituitary lesions detected on dMRI may be coincidental and may occasionally lead to unnecessary pituitary resection; hence, these lesions need to be reanalyzed using other complementary diagnostic procedures.

Dynamic biological tests aimed at differential diagnosis of ACTH-dependent CS include the HDDST, CRH test, and DDAVP test. Among these, the CRH test is most recommended. Recently, Frete et al. suggested a new diagnostic strategy for CD. The combination of CRH, DDAVP, MRI, and thin-slice whole-body CT achieved a high diagnostic accuracy for CD, thus reducing the need for BIPSS [21, 22]. However, CRH is still not available in many countries, and hence, HDDST is still commonly used in the differential diagnosis of ACTH-dependent CS in such regions. Though the accuracy of this test may be compromised by various factors, the major problem with HDDST is its diagnostic inaccuracy [23–25]. In all cases, the response is related to the original cortisol secretion rate; greater suppression is usually observed in patients with lower basal cortisol levels. Some patients with severe CD, particularly those with large tumors and extremely high levels of cortisol, may lack response, whereas at least 10% of patients with EAS have a positive response [5]. The significant overlap in the

![ROC curves](image)

**Fig. 2** ROCs for the HDDST, dMRI, and the combined of HDDST and dMRI
responses of CD and EAS to HDDST compromises the diagnostic accuracy of this test. According to Aron et al., the sensitivity of the HDDST for the diagnosis of CD was 81.0% and the specificity was only 66.7% [23]. A more recent study evaluated 85 patients with CD and 10 patients with EAS. The sensitivity and specificity of the HDDST were 79 and 80%, respectively [26]. Though HDDST is widely used, different sensitivities and specificities have been reported in different studies. Patients with EAS in series may be a factor affecting the assessment. In our study, using a generally accepted cut-off of 50% suppression, the sensitivity and specificity of HDDST were 70.3 and 77.8%, respectively. To avoid the bias of predetermined criteria, we constructed an ROC for the HDDST and found that more than 42.5% suppression of cortisol levels had the highest accuracy, with a sensitivity of 76.2% and a specificity of 77.8%. The diagnostic accuracy was still lower than that of dMRI. Thus, our data also supported that the HDDST has a poor diagnostic performance and cannot help establish the differential diagnosis alone.

Though the diagnostic performance of HDDST alone was not sufficient, the combination of pituitary dMRI and HDDST (both positive) achieved a high specificity of 94.4% and a positive predictive value of 98.4% in distinguishing between patients with CD from those with EAS. Moreover, the combination of both tests in the present study showed a specificity similar to that of BIPSS, according to previous studies [27–30]. The data presented here suggest that patients with a positive finding on pituitary dMRI and a positive HDDST result do not require to undergo BIPSS to confirm the diagnosis of CD. For patients with either discordant or negative dMRI and HDDST results, making a diagnosis is difficult. BIPSS is recommended according to the currently recommended algorithms. However, Frete et al. recently suggested a new strategy to reduce the need for BIPSS, recommending whole-body CT prior to BIPSS in case of discordant pituitary MRI and endocrine tests results [21]. This recommendation shows potential and needs further investigation.

Three patients were incorrectly diagnosed with CD and submitted to TSS in our study. One patient had a positive finding on pituitary dMRI and a positive HDDST result, and the other two patients had negative findings on pituitary dMRI but positive HDDST results. This suggests that caution needs to be exercised when deciding to perform surgery. The introduction of new diagnostic methods may help improve the accuracy of diagnosis and thus needs to be further researched.

In addition, our study showed that the combined criteria of greater than 68% of suppression on the HDDST and/or a positive finding on pituitary dMRI provide a sensitivity of 86.1% and a specificity of 83.3%, which were superior to HDDST or dMRI alone. Notably, the diagnostic accuracy is based on the present series; therefore, validation is required to apply this criterion to clinical practice.

This study has some limitations. First, a selection bias may have occurred since we excluded patients who did not undergo surgery. Moreover, a considerable number of patients with EAS may have been excluded because their condition could not be confirmed surgically or pathologically. Second, dexamethasone levels were not measured in patients undergoing the HDDST. When using the HDDST, we assumed that the test procedure was performed accurately and that the administration and metabolism of dexamethasone were correct. However, in clinical practice, the concomitant use of commonly prescribed medications may alter dexamethasone metabolism and impair diagnostic efficacy [31]. The diagnostic accuracy could also be affected by the bioavailability of dexamethasone owing to improper intake by some patients [32]. Therefore, improved measurement of dexamethasone is needed.

In summary, pituitary dMRI was superior to HDDST in the differential diagnosis of ACTH-dependent CS. Though the diagnostic performance of the HDDST alone was unsatisfactory, the combination of HDDST and pituitary dMRI achieved higher specificity. Therefore, HDDST should be used in combination with pituitary dMRI to establish a diagnosis.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The written informed consent was obtained from all patients that enrolled.

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