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A survey of clinical practice patterns in diagnosis and management of Cushing's disease in Iran

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Abstract

Background: Cushing's disease is the most prevalent cause of endogenous adrenocorticotrophic hormone hypersecretion. The aim of this study was to document the current clinical practice pattern in the management of Cushing's disease by Iranian Endocrinologists to determine their opinions and compare them with the current clinical practice guidelines.

Methods: An eight-item questionnaire dealing with diagnosis, treatment and follow up of patients with Cushing's disease was developed, piloted, and sent to the members of Iranian Endocrinology Society.

Results: Among 90 endocrinologists invited to participate in the survey, 76 replied. Most respondents selected overnight dexamethasone suppression test (ONDST) and assessment of 24-hour urinary free cortisol (UFC) as the best screening tests followed by midnight serum cortisol and midnight salivary cortisol. Classic high dose dexamethasone suppression test and measurement of serum ACTH were selected for localization of the primary lesion by 64.5%. The primary choice of treatment was trans-sphenoidal pituitary surgery (86.8%). For the recurrence of Cushing's disease, the preferred treatment modality was medical therapy followed by bilateral adrenalectomy, and pituitary re-surgery. In case of treatment failure after the first pituitary surgery and ketoconazole treatment, 51% chose bilateral adrenalectomy, while36.8% selected pasireotide only.

Conclusion: ONDST and UFC are two most common tests used to screen an index case with signs and symptoms of hypercortisolism. The primary choice of treatment in Cushing's disease is pituitary surgery. However, medical treatment by ketokonazol is preferred for the recurrences. Pasireotide is the second alternative after bilateral adrenalectomy in case of treatment failure after pituitary surgery and ketoconazole.

Keywords: Cushing's disease, Diagnosis, Management, Clinical Practice.

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Introduction

Excessive secretion of adrenocorticotrophic hormone (ACTH) by a pituitary corticotroph adenoma is the most prevalent cause of endogenous Cushing's disease. Elevated ACTH secretion plus disturbed hypothalamic-pituitary axis result in excess cortisol production from adrenal glands and subsequent clinical features of hypercortisolism (1).

The aim of treating Cushing's disease has been to reverse clinical feature, normalize biochemical derangement, and achieve long-term disease free survival (1).

The diagnosis and management of Cushing's diseaseis challenging for clinicians. The American Endocrine Society and European Society of Endocrinology published an evidence-based clinical practice guideline in 2008 (2). Measurement of cortisol in serum, urine, or saliva is the target for diagnosis. The main recommended investigations are urinary free cortisol (UFC), overnight 1 mg and two-day 2 mg/day dexamethasone suppression tests (DST), and late-night salivary cortisol. The optimal treatment for ACTH producing tumor is surgical resection. However, in case of surgical failure or relapse, second line options include medical therapy, repeated pituitary surgery, radiotherapy, and bilateral adrenalectomy (3,4).

The aims of this survey were to document the current clinical practice in the diagnosis and management of Cushing's disease by Iranian endocrinologist and to compare the current practice with the recommendations of the Endocrine Society Clinical Practice Guideline.

Methods

The survey comprised of questions in relation to diagnosis, treatment, and follow up of an index case with symptoms and signs of Cushing's disease (Table 1). Some questions required a single best response to be selected from a list of multiple choices. Questions related to the diagnosis of etiology of Cushing's disease allowed multiple items to be selected simultaneously. All possible answers were included for each question in order to decrease the bias. The questionnaire was appraised by the members of a scientific committee and comprised of 9 endocrinologists, expert in diagnosis and management of Cushing's disease. The target group was the clinically active Iranian endocrinologists in diagnosis and management of patients with Cushing's disease. Survey responses were collected anonymously.

Table 1. The index case: A Female with cushing syndrome

A 32-yr-old woman presents with fatigue and weight gain since six months ago. She also complaints of oligomenorhea and slowly progressive hirsutism. She is otherwise healthy and take no medication except of captopril for hypertension. Her BP is 135/87mmHg and has a FG score of 12, as well as purple striae over the flanks and lower abdomen. Fasting blood glucose level is 130mg/dl.

Statistical Analysis

Data were analyzed anonymously. As all participants did not answer all questions, the valid percent was calculated individually for each question. Data were expressed as frequency tables (n, %) and proportion.

Results

Response Rate and Respondent Characteristics

Ninety endocrinologists were invited to participate in the survey; 76 (84.4%) participated, and 53 (69.7%) answered all questions. Thirty eight (50%) respondents were endocrinologists who were residing in Tehran (the capital city), and 38 (50%) were from other provinces. The majority of the respondents visited less than 10 newly diagnosed patients with Cushing's disease annually. Baseline characteristics of the participants are presented in Table 2.

Diagnostic Evaluation of the Index Case

Assessment of 24-hour urinary free cortisol (UFC) and fasting serum cortisol after an overnight dexamethasone suppression test (ONDST) has been obtained by 57 (75%) and 66 (86.8%) of the respondents,

Table 2. Baseline characteristics of the participants

Age (mean ± SD)		47.43 ± 5.36
Years after graduation (mean ± SD)		8.23 ± 4.90
Annual No. of visited patients (%)	<10	89.2%
	10-15	9.2%
	>15	1.5%
Location of clinical practice	University clinic	80.3%
	Private clinic	10 %
	Public clinic	8.7%

respectively. Forty five (59%) respondents selected both of the above screening tests simultaneously; only 9.2% of the respondents obtained UFC as a single screening test, and 22.4% selected ONDST as the best single screening test. Moreover, measurement of midnight serum cortisol was selected by 15 (19.7%) respondents. Midnight salivary cortisol in combination with the other tests was obtained by 7.9% of the respondents.

Figure 1-A demonstrates the percentage of respondents ordering the listed laboratory tests for the index case. Considering the assessment of current clinical practice for localizing the primary lesion, classic high dose dexamethasone suppression test may be obtained alone by 17 (22.4%). Forty

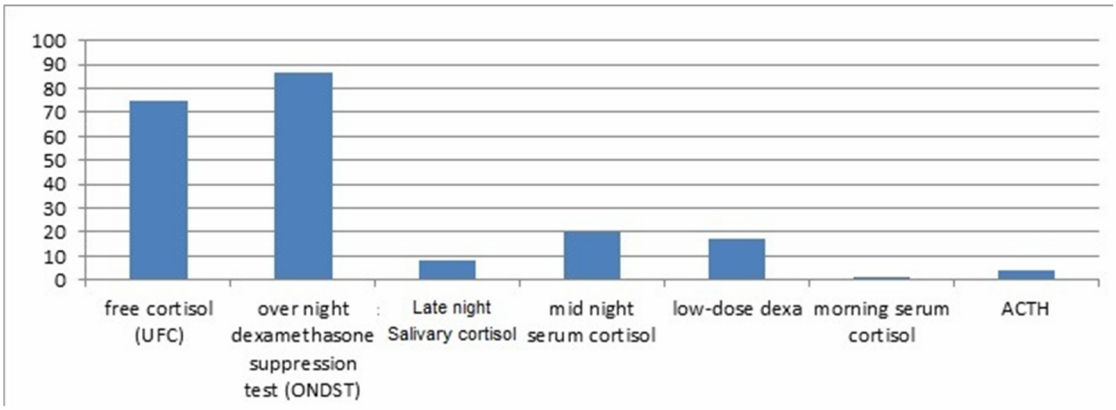

Fig. 1 A.

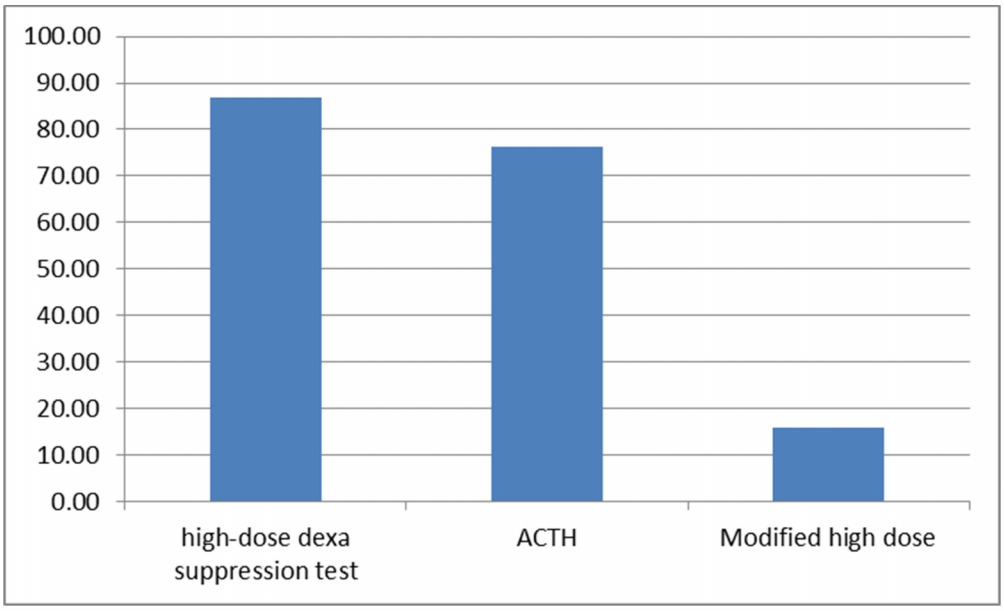

Fig. 1 B.

Fig. 1. Percentage of respondents who would select the listed laboratory tests for screening (A) or localization (B) in a patient with clinical evidence of hypercortisolism

nine (64.5%) respondents indicated the use of both serum ACTH and classic high dose dexamethasone suppression test, while 12 (15.8%) respondents selected modified high dose dexamethasone suppression test for localizing the primary lesion (Fig. 1-B).

The respondents were also asked to provide their diagnostic approach if the preliminary evaluations were indicative of an ectopic Cushing's disease. Of the respondents 71 (93.4%) selected a high resolution CT scan of thorax, and 63 (82.9%) selected a spiral CT scan of the abdomen; 58 (76.3%) said they would use both tests to assess an ectopic source; 53 (69.7%) of the respondents selected anoctreotide scan, while 9 (11.8%) chose to use inferior petrosal sinus sampling.

Treatment

Use of Surgical and Medical Alternatives

The participants were asked to specify their primary choice of treatment in an index case of ACTH dependent Cushing's disease with a 6 mm pituitary adenoma reported in dynamic brain MRI. Transsphenoidal pituitary surgery (TSS) was selected by 66 (86.8%)of the respondents; 4 (5.3%)and 1 (1.3%) respondents preferred ketoconazole, and cabergoline, respectively; and five of the respondents (6.6%)chose long acting somatostatinanalogues, metyrapone, mitotane, or bilateral adrenalectomy.

Recurrence of Cushing's Disease

The index case was operated through a TSS approach and no evidence of hypo or hypercortisolism was found for the next two years after the operation when recurrence happened that proved to be ACTH-dependent. However, there was no evidence of pituitary adenoma and/or ectopic source for the elevated ACTH in the diagnostic evaluations.

The respondents were then asked to specify their next options in treating the index case.

Of the respondents, 39 (51.3%) chose medical treatment as the preferred treatment modality for the recurrence of Cushing's disease in this clinical setting, 24 (31.6%) preferred bilateral adrenalectomy, and 14 (18.4%) favored pituitary re-surgery.

In the case scenario, the index case was treated by ketoconazole. However, three months after the initiation of ketoconazole, liver enzymes rose to five time upper limit of the normal range. The participants were then asked to select their choice of action. The preferred treatment for Cushing's disease after pituitary surgery and ketoconazole failure was bilateral adrenalectomy (39 (51.3%)) and pasireotide (28 (36.8%)). Seven endocrinologists (9.2%) selected combination therapy with cabergoline and pasireotide, and only 4 (5.3%) ordered another pituitary surgery.

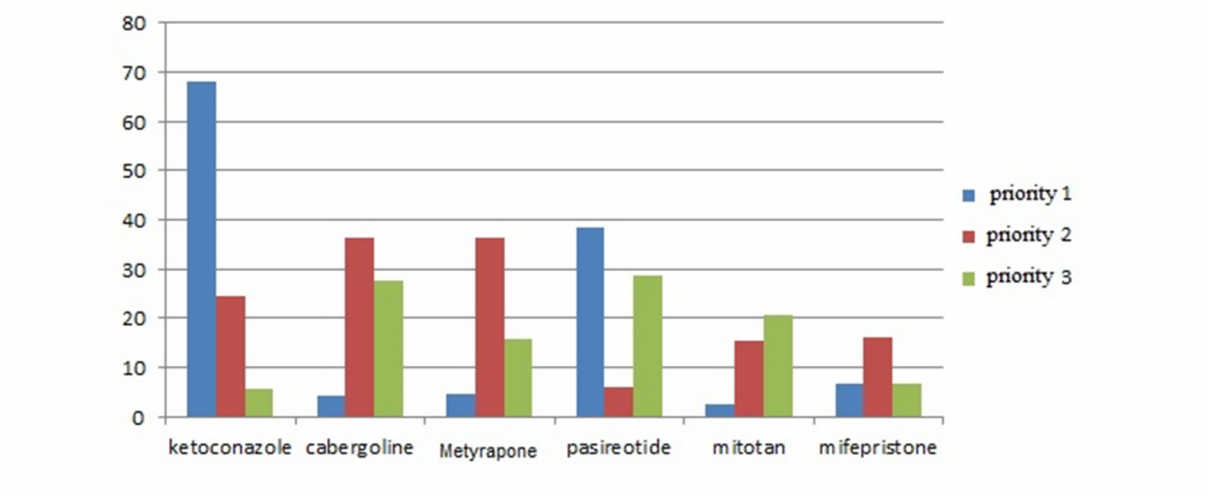

Fig. 2. Medical therapy priorities

Considering the available treatment options, the respondents were asked about the rate of success in the treatment of ACTH dependent Cushing's disease in Iran. Thirty seven (48.7%) reported a success rate of 30-49%, and 29 (38.2%) believed this rate seemed high (50-79%).

They were also asked to give priority to a list of drugs they would like to be available for treating Cushing's disease in Iran; 67.9% of the respondents selected Ketoconazole as their first drug of choice while 38.5% chose Pasireotide (Fig. 2).

Discussion

This study represents the first national survey to assess the current clinical practice in the diagnosis and management of Cushing's disease.

The results revealed that the majority of Iranian endocrinologists would choose ONDST and UFC as screening tests. It was also found that they prefer trans-sphenoid pituitary surgery for those patients who have pituitary dependent source for hypercortisolism. However, when the first pituitary surgery fails, ketoconazole was the treatment of choice. In the case of treatment failure with pituitary surgery and ketoconazole, novel medical treatments such as pasireotide was selected by more than one third of the participants, while bilateral adrenalectomy was preferred by a half.

The diagnostic trends identified in this study are compatible with the recommendations of Endocrine Society Clinical Practice Guideline on the diagnosis of Cushing's diseasein 2008 (2).The guideline indicates that there is no single best screening test for Cushing's disease. Random serum cortisol or plasma ACTH is not recommended for screening. Moreover, 24-hour UFC, late night salivary cortisol, 1mg ONDST, and longer low dose DST were offered for the initial investigation. In this survey, only few participants selected random serum cortisol and plasma ACTH. Furthermore, measurement of late night salivary cortisol was not popular as the initial investigation. Salivary cortisol represents the active form of serum cortisol which is not affected by the flow rate of saliva (5,6). As the salivary glands express 11β-hydroxy steroid dehydrogenase type 2, licorice or using tobacco may produce a false positive result (7,8).

In this survey, the small number of participants selected late night salivary cortisol for the initial investigation and this may have been due to the unavailability of the test. More traditional tests such as ONDST and 24-hour UFC have been available for the past several years. Therefore, the majority of the endocrinologists are familiar with their use in clinical practice.

Considering the treatment pattern, surgical removal of the pituitary adenoma by a trans-sphenoidal approach is the first line treatment for Cushing's disease (3). The remission rate for microadenomas was reported to be 65-90%, with a recurrence rate of 10-20% at 10 years (9,10).

The majority of the respondents in this survey selected TSS as the primary choice of treatment in an index case with ACTH dependent Cushing's disease due to pituitary microadenoma. However, after a proven recurrence, medical treatment with ketoconazole was the preferred choice of action by half of the participants although bilateral adrenalectomy was selected by a third.

Medical treatment has gained a significant space during recent years in treatment of Cushing's disease. It might be performed prior to the surgery to reduce the risk of procedure, or control the metabolic consequences of high serum cortisol (11). Furthermore, medical treatment could reduce hypercortisolism and should be considered before bilateral adrenalectomy.

Bilateral adrenalectomy provides an immediate control of hypercortisolism. However, lifelong glucocorticoid and mineralocorticoid replacement may be necessary (12). Although the second-line treatment for recurrence of Cushing's diseaseshould be individualized, bilateral adrenalectomy is indicated when hypercortisolism persisted despite medical therapy (13).

Ketoconazole is an inhibitor of cortisol production by its action on 11β-

hydroxylase. The average remission rate for patients with Cushing's disease is 70% (14).The reversible elevation of liver enzymes occurs in 5-10% of the patients and serious hepatic injury has been reported in 1 out of 15000 cases (15).

In this study, pasireotide was selected by more than a third of the respondents when a patient experiences treatment failure with pituitary surgery and ketoconazole.

Recent studies demonstrated that somatostatin receptor subtype 5 (SSt5) and dopamine receptor subtype 2 are frequently expressed by corticotroph adenomas (16-21). Octreotide, a somatostatin analogue (SSA) with binding affinity to somatostatin type 2 receptors does not have suppressive action on ACTH (22-23). Pasireotide that binds to SSt5 was reported to normalize UFC in 15% and 26% of patients with Cushing's disease after six months of therapy with a dose of 600 µg and 900 µg, respectively. Drug induced hyperglycemia is the major adverse event reported in the majority of the patients. Diarrhea, nausea, and abdominal pain are other most common events observed with pasireotide treatment (24).

This survey provided an opportunity to evaluate the current clinical practice in the diagnosis and treatment of Cushing's disease in Iran. However, potential selection bias may happen when including clinically active endocrinologists in the management of Cushing's disease.

In conclusion, our survey showed that traditional ONDST and 24 hour UFC are still the most popular tests for the initial investigation of a patient with symptoms and signs of hypercortisolism.

Considering the treatment pattern, transsphenoidal pituitary surgery is the treatment of choice in Cushing’s disease, while ketoconazole is the preferred medication in case of recurrence. Moreover, pasireotide is second to bilateral adrenalectomy when pituitary surgery and ketoconazole fail to treat the patient.

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Conflict of interest

The authors declare that they have no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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