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Case study

Root cause analysis of diagnostic and surgical failures in the treatment of suspected Cushing's disease

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ABSTRACT

Cushing's disease (CD) is a condition characterized by excess glucocorticoid from an ACTH pituitary adenoma. Identifying surgical candidates represents a major diagnostic challenge. We performed a root cause analysis (RCA) of treatment failures for patients with suspected CD. The present study aims to categorize failures in treatment. Medical records were reviewed from 2008 to 2017 for all patients treated surgically for suspected CD. Demographics, past medical history, endocrine outcomes, imaging findings, laboratory studies and clinical features were collected. Eighty-five patients were identified with preoperative suspicion for CD. Thirty-four (40.0%) had undergone prior surgery confirming ACTH adenoma, leaving 51 (60.0%) for analysis. The average length of follow-up was 18.3 ± 24.1 months, 42 (82.4%) patients had postoperative biochemical remission of hypercortisolism. Forty-three (84.3%) had histologically confirmed CD, two (3.9%) were diagnosed with extracranial ACTH-secreting tumors, four (7.8%) had no obvious tumor upon intraoperative exploration, one (1.9%) had suspected pituitary ACTH hyperplasia, and one (1.9%) had no identifiable pathologic tissue despite apparent gross tumor observed during surgery. Thirty-four (66.7%) patients had remission following surgery alone, four (7.8%) after reoperation, and four (7.81%) after radiosurgery. One patient (1.9%) was found to have an ectopic source of ACTH, and one (1.9%) had immunohistochemically confirmed adrenal tumors. On RCA, we identified six categories of treatment failures. CD is a diagnostic challenge that can be difficult to distinguish from other forms of hypercortisolism. Surgical efficacy can be improved with more accurate patient selection, and perhaps with improved imaging methods.

1. Introduction

Cushing's disease (CD) is a rare disorder that remains notoriously difficult to diagnose despite a thorough preoperative evaluation [1–5]. The difficulty in diagnosing this illness arises in part from its broad, non-specific presentation. Although some patients are classically "Cushingoid," others demonstrate few of the characteristic signs and symptoms. General malaise, obesity, and muscle weakness—all hallmarks of CD—are broadly present in many conditions. Other symptoms, including excessive sweating and body hair, anxiety, depression, easy bruising, and irritability are difficult to diagnose, are not immediately alarming to patients, or arise slowly enough that they are only identified in retrospect [5–8]. Furthermore, laboratory diagnosis is not entirely accurate and often is confusing.

Even when the constellation of symptoms is identified as consistent with CD, serum testing for hypercortisolism remains imprecise. Reasons for this include the physiologic diurnal cycle of serum cortisol, iatrogenically elevated cortisol in the case of patients treated with long-term steroids for chronic illness, and patient compliance with diagnostic test instructions. More specific diagnostic tests, such as low- and high-dose dexamethasone suppression tests or urine free cortisol tests, are complicated and require patients to submit to longer testing. Salivary cortisol determinations, another recommended screening test for CD, can be falsely elevated in patients who exercise or eat later in the evening, or who are shift laborers. If ACTH-dependent hypercortisolism is suspected after the above tests, inferior petrosal sinus sampling (IPSS) is often performed to confirm a primary versus ectopic secondary source of ACTH, but can also be inconclusive if not performed in a systematic fashion [3,9–11].

The diagnosis of CD is complicated even after hypercortisolism is firmly established. ACTH-secreting lesions in the pituitary region are often prohibitively small for adequate visualization on magnetic resonance imaging, and ectopic sources of ACTH, such as

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tumors of the adrenal glands or, more rarely, the lungs, are also possible [2–4,12–14]. In many cases, even when a central source of excess ACTH is suspected after the above diagnostic tests, no lesion is present on imaging [15,16].

In patients with confirmed CD, transsphenoidal resection of the ACTH-secreting lesion is the standard of care [1,5,15,17–20]. Reported rates of initial remission after surgical intervention range from 69% to 98% [19]. In cases where patients fail to enter remission after surgical resection, several additional options are available, including re-exploration of the parasellar, suprasellar, and suprachiasmatic regions, reexploration of the interior of the pituitary itself, targeted resection of the central mucoid wedge, hemihypophysectomy or adjuvant radiation of the pituitary region [21–27]. In cases where surgical cure is still not achieved and patients are debilitated from chronic cortisol exposure, including intractable hypertension with end-organ damage and labile serum glucose despite maximal medical therapy, patients may be candidates for a subtotal hypophysectomy or bilateral adrenalectomy [15,19,23,28–30]. Medical therapy is a second line treatment for CD, is often indicated in patients who are refractory to surgical treatment, and can be effective in reducing hypercortisolism and improving symptoms [7,31–33].

Contemporary reports in the literature have indicated that surgical resection in patients with confirmed CD often leads to resolution of hypercortisolism [1,19,23,34]. In this paper, we aim to identify the actuarial remission rates for patients presenting with symptoms suggestive of central ACTH excess and treated with surgical resection, regardless of whether their pathological diagnosis confirmed CD, and to report a root cause analysis of surgical failures for CD.

2. Methods

Medical records from Brigham and Women's Hospital were retrospectively reviewed from April 2008 to July 2017 for all patients treated by the senior author for suspected CD, regardless of final, post-operative diagnosis. These patients were all referred by outside practitioners, including neurosurgeons, endocrinologists, and primary care providers, for evaluation of possible CD. Relevant variables, including demographic data, past medical history, endocrine outcomes, imaging findings, clinic notes, laboratory studies and intraoperative findings, were collected. Patients with prior surgery were eliminated from final analysis. Data analysis was performed using IBM® SPSS® Version 22 (IBM SPSS Inc., Armonk, New York).

3. Results

Eighty-five patients with diagnostic testing suspicious for CD from April 2008 to July 2017 were identified. Of these patients, 34 (40.0%) had a prior operation that pathologically confirmed an ACTH-secreting pituitary adenoma, and were therefore excluded from analysis. Of the 51 patients remaining, 43 (82.4%) had histologically confirmed CD (ACTH producing adenoma of the pituitary gland) post-operatively. Two (3.9%) had an extracranial source of ACTH-secreting tumor, four (7.8%) had no obvious tumor intraoperatively nor on pathology, one (1.9%) had a diagnosis of pituitary hyperplasia, and one (1.9%) did not have any identifiable pathologic tissue despite gross findings of a tumor on operative exploration (Table 1).

Patients treated for suspected CD underwent a thorough diagnostic workup pre-operatively, including inferior petrosal sinus sampling in 21 (41.2%), computed tomography scan of the chest, abdomen, and pelvis (CT C/A/P) in twelve (23.5.0%), octreotide scans in two (3.9%), and serum CRH and PET scans in one each (1.9%) (Fig. 1). The mean preoperative fasting serum cortisol in all patients preoperatively was 26.7 ± 18.7 ug/dL, the mean late night salivary cortisol was 31.2 ± 65.9 ug/dL, and the mean 24 h urine free cortisol was 289.1 ± 332.6 ug/dL (Table 2). On preoperative MRI, eleven patients (21.5%) had no obvious pituitary or parasellar lesion.

At an average last follow up of 18.3 ± 22.6 months, 42 (82.4%) patients had biochemical evidence of remission of CD. Thirty-four (66.7%) patients had remission of hypercortisolism with endo-

Table 1
Patient Characteristics, Past Medical History and Symptoms, Univariate Analysis.

	Total	Confirmed CD	CD not Confirmed	p-value
No. of Patients (%)	51 (100)	43 (84.3)	8 (15.7)	–
Mean Age (in years)	38.5 ± 15.1	37.3 ± 13.9	44.8 ± 16.3	0.71
Male, no. (%)	17 (33.3)	16 (37.2)	1 (12.5)	0.18
BMI	34.7 ± 9.7	33.8 ± 9.5	38.1 ± 7.7	0.24
Preoperative Sx, no. (%)				
Visual Deficits	5 (9.8)	5 (11.6)	0 (0)	0.31
Hypopituitarism	5 (9.8)	5 (11.6)	0 (0)	0.31
Osteoporosis on DEXA Scan	10 (19.6)	6 (14.0)	4 (50.0)	0.02*
Hyperpigmentation	16 (31.4)	13 (30.2)	3 (37.5)	0.68
Headaches	13 (25.5)	12 (27.9)	1 (12.5)	0.36
Apoplexy	0 (0)	0 (0)	0 (0)	–
Weight Gain	41 (80.4)	36 (83.7)	5 (62.5)	0.16
Neck Fat Deposition	33 (64.7)	28 (65.1)	5 (62.5)	0.82
Muscle Wasting	13 (25.5)	10 (23.3)	3 (37.5)	0.40
Hirsutism[a]	27 (52.9)	21 (48.8)	6 (75.0)	0.17
Classic Cushingoid Appearance	34 (66.7)	29 (67.4)	6 (75.0)	0.67
Past Medical Hx, no. (%)				
Diabetes Mellitus	13 (25.5)	10 (23.3)	3 (37.5)	0.40
Hypertension	30 (58.8)	25 (58.1)	5 (62.5)	0.82
CAD	1 (1.9)	1 (2.3)	0 (0)	0.66
CVA	0 (0)	0 (0)	0 (0)	–
Hyperlipidemia	7 (13.7)	5 (11.6)	2 (25.0)	0.31
Tobacco Use	7 (13.7)	6 (14.0)	1 (12.5)	0.91

* P-value significant <0.05. Two tailed *t*-test. BMI, Body Mass Index; Rx, medication; LFU, last follow-up; Sx, symptoms; Meds, medication.
[a] Among Female patients.

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