



ORIGINAL ARTICLE

Results of repeat transsphenoidal surgery in Cushing's disease. Long-term follow-up



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KEYWORDS

ACTH-secreting
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Hypophysectomy;
Repeat surgery;
Recurrence

Abstract

Objective: Transsphenoidal surgery (TSS) is the treatment of choice for Cushing's disease (CD). However, the best treatment option when hypercortisolism persists or recurs remains unknown. The aim of this study was to analyze the short and long-term outcome of repeat TSS in this situation and to search for response predictors.

Patients and methods: Data from 26 patients with persistent ($n = 11$) or recurrent ($n = 15$) hypercortisolism who underwent repeat surgery by a single neurosurgeon between 1982 and 2009 were retrospectively analyzed. Remission was defined as normalization of urinary free cortisol (UFC) levels, and recurrence as presence of elevated UFC levels after having achieved remission. The following potential outcome predictors were analyzed: adrenal status (persistence or recurrence) after initial TSS, tumor identification in imaging tests, degree of hypercortisolism before repeat TSS, same/different surgeon in both TSS, and time to repeat surgery.

Results: Immediate postoperative remission was achieved in 12 patients (46.2%). Five of the 10 patients with available follow-up data relapsed after surgery (median time to recurrence, 13 months). New hormone deficiencies were seen in seven patients (37%), and two patients had cerebrospinal fluid leakage. No other major complications occurred. None of the preoperative factors analyzed was predictive of surgical outcome.

Conclusions: When compared to initial surgery, repeat TSS for CD is associated to a lower remission rate and a higher risk of recurrence and complications. Further studies are needed to define outcome predictors.

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PALABRAS CLAVE

Adenoma hipofisario
productor de
hormona
adrenocorticotropa;
Síndrome de Cushing;
Hipofisectomía;
Reintervención;
Recidiva

**Resultados de la reintervención quirúrgica en la enfermedad de Cushing.
Seguimiento a largo plazo****Resumen**

Objetivo: La cirugía transesfenoidal (TE) es el tratamiento de elección en primera línea en la enfermedad de Cushing (EC). Sin embargo, se desconoce cuál es el tratamiento más adecuado cuando el hipercortisolismo persiste o recidiva. El objetivo del estudio es analizar el resultado a corto y largo plazo de la reintervención TE e identificar factores predictores de respuesta.

Pacientes y métodos: Se revisaron retrospectivamente los datos de 26 pacientes con hipercortisolismo persistente (n=11) o recidivado (n=15) reintervenidos por un mismo cirujano entre 1982 y 2009. Se consideró remisión a la normalización del cortisol libre urinario (CLU) y recidiva a la presencia de CLU elevado después de una remisión. Como potenciales predictores de respuesta se analizaron los siguientes factores: función adrenal tras la cirugía inicial (persistencia o recidiva), visibilidad del tumor en las pruebas de imagen, grado de hipercortisolismo antes de la reintervención, mismo/diferente cirujano en ambas cirugías y tiempo hasta la reintervención.

Resultados: Doce pacientes remitieron inmediatamente tras la reintervención (46,2%). De los 10 con seguimiento a largo plazo recidivaron 5 (mediana de tiempo hasta la recidiva: 13 meses). Se indujeron nuevos déficits hormonales en 7 pacientes (37%) y fístula de líquido cefalorraquídeo en 2. No se observaron otras complicaciones. Ninguno de los factores estudiados se asoció con la respuesta.

Conclusiones: Comparada con la cirugía inicial, la reintervención TE en la EC se asocia con una menor tasa de remisión y un riesgo mayor de recidivas y complicaciones. Son necesarios más estudios para definir factores predictores de respuesta.

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Introduction

Transsphenoidal surgery (TSS) is the treatment of choice in Cushing's disease (CD) since it enables complete resection of the tumor while preserving the rest of the pituitary function with a low morbidity rate. This approach leads to immediate remission of hypercortisolism in 70–85% of the patients when carried out by an experienced neurosurgeon.¹ However, about 10–25% of these patients will recur within the following 10 years.^{1–5}

When hypercortisolism persists or recurs after initial TSS, several treatment options have to be considered, including repeated TSS, pituitary radiotherapy, medical treatment or bilateral adrenalectomy. Until now, few reports on the results of a repeated TSS in CD have been published, and even less have described the long term outcome, so little is known about recurrence rates.

At our institution the second line treatment, after initial TSS failure, is pituitary irradiation in around 70% of patients. A second TSS is considered when initial TSS has been performed by a non-experienced neurosurgeon or when a visible and accessible tumor remnant is located with magnetic resonance imaging (MRI).

The present study describes the results of repeated TSS at our hospital in patients with persistent or recurrent hypercortisolism.

Patients and methods

Between July 1982 and April 2009, 26 patients with CD underwent repeated TSS by a single neurosurgeon (JG-U) due to the presence of persistent (11 patients) or recurrent (15 patients) hypercortisolism after initial TSS. Persistent

hypercortisolism was considered when the patient had an increased urinary free cortisol (UFC) in the immediate post-surgical evaluation and recurrent hypercortisolism when an elevated UFC was detected following a period of adrenal insufficiency or normocortisolism.

All the patients had been diagnosed with CD before the first surgery based on the following features: absence of a circadian rhythm in serum cortisol, increased UFC excretion, elevated or inappropriately normal ACTH plasma levels, characteristic serum cortisol responses to the administration of dexamethasone (failure to suppress serum cortisol below 1.8 mcg/dl at 8 am following a single dose of 1 mg dexamethasone at 23 h the night before (1 mg DST); and decrease of UFC levels greater than 50% following a 2 mg dexamethasone dose every 6 h for 48 h) and imaging of the sella turcica. Inferior petrosal sinus sampling was performed in 6 patients in whom prior tests were inconclusive.

Before repeated TSS, all patients had clinical features of hypercortisolism which was biochemically confirmed by elevated UFC measurement in every case. At this time, serum cortisol at 8 am (24 patients), serum cortisol at 11 pm (18 patients), ACTH plasma levels (17 patients) and response to the 1 mg DST (18 patients) were also evaluated. In all cases, the results obtained supported the diagnosis. New imaging of the sella turcica with computed tomography (3 patients) or magnetic resonance (MRI) (23 patients) was obtained in every case. Imaging studies did not reveal any lesion in 12 patients; a microadenoma was identified in 10 and remaining tissue of a macroadenoma was evident in 4. Pituitary function, including IGF1 levels but not GH after stimulatory test, was evaluated before reoperation in 22 patients. It was normal in 21 while the other one had an isolated gonadotropin deficiency.

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