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REVIEW ARTICLE

# Cushing's disease in 2012☆

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**Abstract** The aim of this study was to review the literature published and the most important papers presented to meetings on Cushing's disease from October 2011 to September 2012. The selection has been performed according to the authors' criteria. Articles have been classified into five groups: quality of life and perception of the disease, clinical features and pathophysiology, comorbidity conditions, diagnosis, and treatment. The results and conclusions of each publication are discussed.


**PALABRAS CLAVE**
Cushing;
Hipercortisolemia;
Calidad de vida

**La enfermedad de Cushing en 2012**

**Resumen** El objetivo de este trabajo es una revisión de los trabajos publicados y las principales comunicaciones a congresos sobre la enfermedad de Cushing desde octubre de 2011 a septiembre de 2012. La selección de los trabajos se ha realizado bajo el criterio de los autores y han sido agrupados en los apartados siguientes: percepción de la enfermedad y calidad de vida, clínica y fisiopatología, comorbilidades, diagnóstico y tratamiento. Se comentan los resultados y las conclusiones de cada trabajo.


## Introduction

Cushing's disease (CD) is derived from an ACTH-secreting pituitary tumor that causes increased cortisol secretion. CD is a severe disease, potentially fatal due to significant comorbidities, which greatly impairs quality of life. The diagnosis of both hypercortisolism and the origin of excess ACTH in CD is very difficult. Although surgical treatment is required, pituitary surgery is not successful in all cases and other treatment options should be used.

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This review focuses on a selection of advances published and reported from the end of 2011 to September 2012.

## Perception of the disease and quality of life

Health-related quality of life has been recognized as a significant aspect in CD management. The first quality of life questionnaire specific for CD, CushingQol,[1] has been available since 2008. Tiemensma et al.[2,3] published two articles about the perception of the disease. The first article reported a close correlation between quality of life and disease perception, with much poorer indices than those recorded for other conditions characterized by chronic pain. In a second study, the authors used the patients' perception of their body image, as reflected in drawings, to compare differences before and after treatment. Two significant conclusions were drawn from these studies, applying to quality of life impairment itself, and to the prolongation of such impairment after disease remission has been achieved.

The most relevant publication related to quality of life consists of the development of a new methodology specifically for CD, the Tuebingen-CD25.[4,5] The final version consists of 25 items grouped into six subcategories accounting for 72% of the variance of quality of life in CD: depression, sexual activity, interaction with ones surroundings, eating behavior, body disability, and mental capacity.

This impairment follows a bimodal distribution, so that it is greater in people aged under 31 years and between 51 and 60 years, while it is lower in people aged 31–50 years and in those over 60 years of age.

Quality of life is not related to cortisol or ACTH levels, except for urinary free cortisol (UFC) for the subcategories of eating behavior, mental agility, and concentration capacity.

In a second study, the authors established reference values using an age- and sex-matched adult population. Moderate and severe quality of life impairment was found in 25% and 41% respectively. As regards the reference population, moderate or severe impairment was found in approximately two thirds of cases in each subcategory. Women showed greater impairment than men.

The authors emphasize that the women had higher scores than men, reflecting a lower quality of life, which in turn affected their social surroundings, sexual activity, physical capacity, and eating behavior. Women showed impairment in all subcategories, while only physical capacity and concentration ability or mental agility were impaired in men. As a limitation of this conclusion, it should be noted that the male population only consisted of 11 patients with CD.

## Clinical signs and symptoms and pathophysiology

Mention should first be made of the Mathioudakis et al. study,[6] which compared hormone activity to tumor size and found no relation between them. The clinical signs and symptoms may be even less marked in big tumors, and it may therefore be difficult to suspect hypercortisolism. In fact, only plasma cortisol levels and cortisol/ACTH ratio are significantly lower in macroadenomas as compared to microadenomas. Less skin fragility and muscle weakness are also seen in bigger tumors. Only headache is more common in macroadenomas.

Pecori Giraldi et al.[7] analyzed this variability in secretory capacity in response to stimulation and suppression tests. They compared 72 ACTH-secreting tumors incubated with CRH or dexamethasone (DXM). Cultures of rat pituitary cells were used as controls. The great variability in the response obtained suggests the existence of multiple phenotypes in patients with CD. Controls did not show this variability.

The authors considered as positive any change greater than 20% as compared to unstimulated samples and found that ACTH increased in 70% of cases at four hours and in 54% of cases at 24 h. ACTH levels increased by more than 50% in only half the patients.

DXM suppression was only greater than 75% in half of the patients, while no change was seen in 30%, and a paradoxal increase was found in 20%.

These results reflect the variability of in vivo responses to CRH and DXM shown by patients with CD.

Desmopressin (DDAVP) is able to stimulate tumoral corticotropic cells, and therefore differentiates CD from a pseudo-Cushing's state. Wang et al.[8] studied responses to DDAVP and CRH before surgery and immunohistochemistry (IHC) to analyze the expression of the CHR receptor (CRHR) and the three subtypes of vasopressin receptor (V1R, V2R, and V3R).

These authors found that V1R, V3R, and CRHR were widely expressed in all patients. By contrast, V2R expression was highly variable and lower in macroadenomas. In vivo ACTH responses to DDAVP correlated to tumor size and expression of V2R, but not V1R or V3R. ACTH response to CRH did not correlate to CRHR expression. The authors suggested that changes in response to DDAVP in CD are due to V2R expression by these tumors.

As regards prognostic and aggressiveness markers in CD, Evang et al.[9] studied cadherin E levels and the expression of its gene. The decreased expression of this membrane protein of epithelial cells was reported in several types of cancer and related to its invasive capacity and the development of metastasis.[10] In somatotropinomas, this low expression has been related to resistance to somatostatin analogues.[11] For IHC, two antibodies recognizing both intracellular and extracellular epitopes have been used. The intracellular domain of cadherin E shows membrane and nucleus staining. This antibody makes it possible to study the fraction of cadherin E bound to the membrane and the fraction internalized to the nucleus. Extracellular domain staining only tests the fraction expressed in the membrane.

Cases are divided into microadenomas, macroadenomas, and Nelson's syndrome, as a reflection of the aggressiveness of the different tumors. A significant difference is seen in nuclear expression, which becomes more intense as aggressiveness increases.

The expression of cadherin E and proopiomelanocortin (POMC) genes has been related to the distribution of staining with the intracellular antibody. The strongest cadherin E expression is found in adenomas predominantly expressed in protein membrane. There are no differences regarding POMC expression.

The authors concluded that CD aggressiveness is characterized by a gradual change in cadherin E expression, which