Cushing's syndrome, main characteristics, different treatments, and outcomes: A single-center study

Síndrome de Cushing, características principales, diferentes manejos y resultados: estudio monocéntrico

ALIN ABREU-LOMBA¹, CARLOS A. SALGADO-CIFUENTES², JENNY P. MUÑOZ-LOMBO², VANESSA BEDOYA-JOAQUI², CINDY V. OSORIO-CORREA³, ADRIÁN A. TABARES-BURBANO², JOSÉ ZAMBRANO-URBANO², ANDRÉS E. DELGADO-TRUQUE², AND NATHALIA BUITRAGO-GÓMEZ^{2*}

¹Endocrinology Unit, Centro Médico Imbanaco, Cali, Colombia; ²Internal Medicine Department, Universidad Libre, Cali Section, Cali, Colombia; ³Endocrinology Department, Salvador Gautier Hospital, Santo Domingo, Dominican Republic

ABSTRACT

Cushing's syndrome is a disorder with unknown prevalence in Colombia and response to available treatments varies. The objective of this study is to evaluate the patients' response to the various treatment options offered, and for this purpose, a retrospective cohort study was conducted with patients diagnosed with Cushing's syndrome. Demographic variables, associated comorbidities, and alternative treatments were reviewed in terms of persistence, remission, and recurrence of Cushing's syndrome. A total of 45 patients met the inclusion criteria, comprising a study group with an average age of 46 years, wherein 60% of patients were female and 47% suffered from hypertension. For all patients, surgery was the first-line option employed. After this initial treatment, 49% experienced remission and 32% recurrence. In the subgroup analyses, Cushing's syndrome patients exhibited 41% remission and 38% recurrence, while the remission rate for patients with adrenal adenoma was 100%, and only one out of the five patients with an ectopic adrenocorticotrophic hormone-secreting tumor experienced remission. (Nevertheless, this single patient had tumor recurrence after remission). In conclusion, the efficacy of the diverse available therapies varies according to the population studied. The demographic characteristics are similar to those reported in the literature.

Key words: Cushing Syndrome. Cushing's disease. Pituitary adrenocorticotrophic hormone hypersecretion. Recurrence. Hypertension.

RESUMEN

El síndrome de Cushing es una patología con prevalencia desconocida en Colombia. La respuesta al tratamiento es variable. Por esta razón, el objetivo de este artículo es determinar la respuesta clínica a las diferentes opciones de tratamiento ofrecidas a estos pacientes. Se realizó un estudio de cohorte retrospectiva en pacientes con diagnóstico de síndrome de Cushing, en quienes se estudiaron variables demográficas, comorbilidades asociadas y tratamientos alternativos en caso de persistencia o recurrencia. Un total de 45 pacientes cumplieron los criterios de inclusión; con un promedio de edad de 46 años, 60% de ellos eran mujeres y 47% hipertensos. Para todos los pacientes, la cirugía fue la primera opción. Un 49% de pacientes tuvo remisión; 32% recurrencia. En el análisis por subgrupos, aquellos con síndrome de Cushing tuvieron un 41% de remisión y 38% de recurrencia. Aquellos con adenoma adrenal tuvieron un 100% de remisión. Solo uno de los 5 pacientes con tumor ectópico secretor de ACTH tuvo remisión, pero posteriormente presentó recurrencia. En conclusión, la eficacia de las diferentes terapias alternativas varía de acuerdo con la población estudiada. Las variables demográficas son similares a las reportadas en la literatura.

Palabras clave: Síndrome de Cushing. Hipersecreción pituitaria de ACTH. Recurrencia. Hipertensión.

Correspondence:

*Nathalia Buitrago-Gómez
E-mail: natybugo@gmail.com

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INTRODUCTION

Cushing's syndrome manifests a series of signs and symptoms, resultant from glucocorticoid overexposure and its effects on peripheral tissues, generating a substantial increase in the development of comorbidities, such as arteriosclerotic cardiovascular disease, osteoporosis, hypertension, and diabetes mellitus, among others¹. Its etiology varies and may be divided into endogenous and exogenous causes². Endogenous causes can be classified as adrenocorticotrophic hormone (ACTH) dependent, averaging 80% of cases, and the remaining as ACTH independent². If left untreated, the mortality rate can be as high as 50% in 5 years; however, patients treated who achieve a long-term total remission experience a survival rate equal to general population³.

The incidence ranges from 0.7 to 2.4 cases/million/year, with a frequency of 39-79 cases/million among various worldwide populations^{3,4}. There is a female-to-male predominance of 3 to 1. The average age at diagnosis for adults is around the fourth decade (younger for females, with a mean of 30.5 years, than males, whose mean is 37.1 years)⁵. For endogenous Cushing's syndrome, treatment depends on the tumor's primary location and the nature of endocrine production thereof, with resection surgery as the first treatment option. Medical treatment is reserved for those tumors which are inoperable⁶. In addition, in the case of Cushing's disease, the first choice of treatment is tumor resection, favoring transsphenoidal surgery (TSS), with a success rate of 90%⁷. The alternative treatments for these patients include a second TSS, radiotherapy, medical treatment with a medication such as pasireotide, metyrapone, mitotane, cabergoline, and ketoconazole. Bilateral adrenalectomy is the last course treatment for an incurable syndrome¹.

Colombia does not have a published register that tracks the scale of the pathology. The objective of this study is to determine the clinical and histopathological characteristics of this disorder, as well as its responsiveness in terms of persistence, remission, and recurrence of the different treatment

options for patients with this syndrome in the city of Cali.

METHODS AND PATIENTS

A retrospective analysis was conducted as of January 1, 2008, up to December 31, 2017, based on the evaluation of the clinical histories of a cohort of patients who had all been diagnosed with Cushing's syndrome and received outpatient treatment at the Centro Médico Imbanaco in the city of Cali. The diagnostic protocol established hypercortisolism through an elevated level of 24 h urinary free cortisol (UFC) measured by chemiluminescent microparticle immunoassay; the upper limit of the normal range was 176 µg/day. Three samples were taken monthly and averaged to obtain this value. Afterward, ACTH dependency was established by elevated baseline or inappropriately normal plasma ACTH levels measured by electrochemiluminescence immunoassay, with 16.7 pmol/L (75 pg/mL) established as the ACTH level upper limit. It was concluded that those patients whose ACTH values were outside the established upper limits suffered from an ACTH-producing tumor. Once these results were established, the subsequent step was to determine the anatomical site of the tumor. The first procedure employed was a pituitary magnetic resonance imaging. If its results were normal, abdominal and thoracic computed tomography (CT) were then performed to identify an ectopic ACTH-producing tumor. Somatostatin scintigraphy or bilateral inferior petrosal sinus sampling was not performed.

For those patients with low or normal ACTH levels, it was concluded their pathology to be ACTH independent and an adrenal imaging with CT was subsequently preformed.

A single high-level pituitary neurosurgeon with a high-volume experience performed all pituitary surgeries.

All patients who had UFC levels below 176 µg/day after therapeutic intervention were considered in remission. The disease was considered recurrent in

Table 1. Basal characteristics of the patients

Patient characteristics	Population n = 45	Interval	Standard deviation
Age			
Mean (SD±)	44 (15.3)	17-76	15.3
Median	46		
Gender			
Female (%)	27 (60)		
Progression time in years (SD±)	6.3	1-44	6.9
Comorbidities (%)			
AHT	21 (47)		
T2DM	8 (18)		
Cardiovascular disease	10 (22)		
Biochemistry			
24 h urinary free cortisol (µg/day)	499.993	198-1307	278.044
ACTH levels at the beginning (pmol/L)	78.386	3-213	47.957
Tumor size mean (mm)			
Hypophysis	12.5	6-40	9.07
Adrenal	14	8-20	4.4
Ectopic	18.4	10-23	5.03
Tumor location (%)			
Hypophysis	32 (71)		
Adrenal	8 (18)		
Ectopic	5 (11)		

AHT: Arterial hypertension, T2DM: Type 2 diabetes mellitus, ACTH: Adrenocorticotrophic hormone, SD: Standard deviation.

patients who, despite having reached the remission criteria, relapsed during their evolution; and it was considered persistent in those patients who, despite the procedure, never achieved remission criteria. All testing were performed by the specialized laboratory at the Centro Médico Imbanaco in Cali. Retroactively, data were gathered based on demographic variables such as age, gender, development time, presence of diabetes, hypertension, and cardiovascular disease due to acute myocardial infarction, heart failure, and stroke. Measured laboratory variables include a 24 h UFC and ACTH blood levels. In addition, other data assessed included the first-line therapeutic option employed, tumor size at the time of first diagnosis, persistence and recurrence of the disease, as well as the second- and third-line therapeutic options with their corresponding percentage of remission.

Statistical analysis

A univariate analysis was carried out to assess the data distribution of numeric variables using the

Shapiro–Wilk test with a significance level $p < 0.005$. A normal distribution was undertaken and summarized utilizing the mean central tendency and dispersion values, as well as the average and standard deviation, respectively. For those wherein an abnormal distribution was observed, these were condensed using the inter-quartile range. The categorical variables were presented as percentages. The data analysis was carried out using the Microsoft Excel and Epidat 4.2 programs.

RESULTS

A total of 45 patients were included in the analysis. The average age at diagnosis was 46 years, with female gender predominance (60%). The average follow-up period was 6.3 years. Hypertension (47%) was prevalent among the comorbidities. Table 1 explains the general population characteristics. The ACTH-producing pituitary tumor was most

Table 2. Pathological findings of the tumors

Pathological findings	Frequency n = 45
Type of tumor	
Pituitary adenoma (%)	32 (71)
Ectopic ACTH-secreting pituitary adenoma (%)	
Lung	4 (9)
Thymus	1 (2)
Cortisol-producing adenoma (%)	8 (18)
Ki 67	
< 1%	15 (33)
> 1% mean (SD $\pm$)	5.9 (4.7) interval: 2-20
Produced hormone (%)	
ACTH	28 (62)
ACTH and prolactin	5 (11)
ACTH and TSH	1 (2)
ACTH and FSH	2 (5)
ACTH, FSH, and TSH	1 (2)
Cortisol	8 (18)

Table 3. Characteristics of ectopic and adrenal tumors

Ectopic and adrenal tumors	n = 13
Age (years)	41
Gender	
Female	5 (38%)
Comorbidities	
AHT	4 (30%)
T2DM	2 (15%)
Cardiovascular disease	1 (7%)
Initial cortisol levels	654
Tumor size mm	15
Ki 67	
<1%	2 (15%)
>1% mean (SD +/-)	5.27 (4.4)
Remission with first treatment	9 (69%)
Recurrence	2 (22%)
Remission after second intervention	4 (67%)
Second recurrence	0 (0%)
Currently in remission	12 (92%)

Table 4. Distribution by gender of comorbidities and type of tumor

Distribution by gender	Male	Female	Total	p value
AHT	7 (39%)	14 (52%)	21	0.393
T2DM	3 (16%)	5 (18%)	8	0.874
Cardiovascular disease	3 (16%)	7 (25%)	10	0.464
Remission	10 (55%)	12 (44%)	22	0.465
Recurrence	3 (30%)	4 (33%)	7	0.867
Type of tumor				
Pituitary adenoma	10 (55%)	22 (81%)	32	0.060
ACTH-producing tumors	3 (16%)	2 (7%)	5	0.333
Adrenal tumors	5 (28%)	3 (11%)	8	0.152
Total	18	27	45	

common (71%). Table 2 summarizes the pathological findings.

Surgical treatment

All patients diagnosed with an ACTH-producing pituitary tumor underwent TSS; of these, only two underwent an extended endoscopic endonasal transsphenoidal approach due to the decisions taken by the performing neurosurgeon. About 71% (32) had TSS and 17% (eight) adrenalectomy. Of the latter, 12% corresponded to ACTH-secreting ectopic

tumors, of which 7% (three) underwent pulmonary lobectomy and 5% (two) underwent thymectomy.

Tables 3 and 4 summarize the subgroups analysis concerning Cushing's disease, ectopic and adrenal tumors.

Medical treatment

As the first-line therapeutic option, 78% (35) of patients did not receive any medication at the time of their diagnosis; eight patients received ketoconazole (18%), whereas 2 patients (4%) received somatostatin

Table 5. Characteristics of Cushing disease subgroup

Cushing disease subgroup	n = 32	Min	Max	SD
Age (years)				
Mean	44	17	76	15
Median	44			
Gender				
Female	22 (68%)			
Evolution time (years)	7,1	1	44	7,6
Comorbidities				
AHT	17 (53%)			
T2DM	6 (19%)			
Cardiovascular disease	9 (28%)			
Starting cortisol level	437	198	1307	240,431
Starting ACTH level	88,2	31	153	29,706
Starting tumor size mm				
At diagnosis	12.5			
Macroadenoma	14 (44%)			
KI 67				
< 1%	13(41%)			
> 1% mean	6.4%	2	20	4.8
Initial medication				
Ketoconazole	6 (19%)			
Current medication				
None	22 (68%)			
Ketoconazole	2 (6%)			
Pasireotide	6 (20%)			
Ketoconazole + cabergoline	2 (6%)			
Remission with first treatment	12 (37.5%)			
Recurrence	4/12 (33.3%)			
Persistence	20 (62.5%)			
Second therapeutic option (24 patients)				
Open surgery	1 (4%)			
Transsphenoidal surgery	17 (71%)			
Pasireotide	3 (13%)			
Ketoconazole	1 (4%)			
Radiosurgery	2 (8%)			
Remission after second intervention	15 (62%)			
Second recurrence	2 (13%)			
Currently in remission	23s (71%)			

analogs; one of the latter received lanreotide (2%), and the other octreotide (2%). At present, the majority of the study group (68%) does not receive any medication; 6% receive ketoconazole; 20% pasireotide; and 6% ketoconazole plus cabergoline. The medical therapy used as second-line treatment option was pasireotide in 13% of cases and ketoconazole in 4% of cases.

With respect to the second-line treatment option for the persisting or recurring cases, 6 patients

(22%) received exclusive medication therapy management.

The nature of the tumors was also evaluated and their characteristics are summarized in table 5. In the subgroup analyses carried out, out of the total number of patients in the study group, 32 had Cushing's disease due to an ACTH-producing tumor; their tumor size did not differ from that of the other subgroups, with an average size of 12.5 mm at the time of diagnosis. All the patients belonging

to this subgroup underwent a transsphenoidal resection, and 6 patients (19%) thereof concurrently received medical therapy with ketoconazole. Of these, 12 (37.5%) achieved remission after surgery; however, 4 patients (33.3%) had a recurrence of the disease. Table 3 summarizes Cushing disease subgroup.

For those patients with an ectopic ACTH-producing tumor, of the five patients with this diagnosis, only one patient was in remission after surgery; however, he later relapsed.

Regarding the eight patients who had a cortisol-producing adrenal adenoma, all patients achieved remission following the adrenalectomy, but two patients subsequently relapsed. Analyzing the combined percentage of patients with ectopic ACTH-producing tumors and cortisol-producing adrenal adenomas, 69% of these patients had a remission of the disease after surgery. However, two of these patients (22%) experienced a later recurrence, requiring a second surgical intervention. Of the latter, 4 patients (67%) experienced total remission after the second intervention, and no patient in this subgroup experienced a recurrence of the disease.

Finally, the remission behavior of the disease was assessed following the second-line intervention. The percentage of patients in remission for the totality of lesions, pituitary tumors, and ectopic tumors was 68%, 62%, and 67%, respectively. The percentages following the second recurrence were 10%, 13%, and 0% for the same variables, respectively.

Table 4 summarizes the distribution by gender, which was found to have no statistical significance.

DISCUSSION

The age of the population in the present study was similar to that in the European Registry on Cushing's syndrome (ERCUSYN)⁸. However, it is important to consider that the age of presentation of the disease varies according to the specific etiology. In addition, it should be noted that the majority of series

published, except for the European one, have described an average lower age of presentation than ours, ranging in general between 28⁹ and 36 years^{10,11} for Cushing's disease and 44 years for ectopic tumors¹². This could be explained by more limited opportunities to access specialized consults and diagnostics and a less active screening for this disease in our country.

Regarding gender, our study established a predominance in the female gender, which is consistent with international literature. However, it is striking that in our series, only 60% were women, which is a much lower female percentage than that reported in other studies, where it commonly ranges somewhere between 69%¹² and 80%^{8,11} even reaching 91%¹⁰. In addition, different subject reviews in this field have described a female-to-male ratio of 3-5:1 in Cushing's disease⁴, others even reaching 3-8:1¹² compared to the 1.5:1 ratio in our study. With regard to ACTH-secreting ectopic tumors, our series found no significant gender differences. In this case, unlike for Cushing's disease, the opposite gender relationship has been found¹³, with a 3:1 male-to-female relationship found over 25 years ago. However, at present, given the increase in tobacco-related lung cancer in females, this relationship is now 1:1¹⁴.

Concerning etiology, our study found that 82% of the cases were ACTH dependent. This is consistent with that described by Lacroix et al. in 2015.⁴ It is worth noting that a high percentage of ACTH-dependent Cushing syndrome is attributed to pituitary adenoma, which corresponds to 71% of cases in our study, consistent with other series, wherein it ranges from 59 to 71% of those cases assessed⁸⁻¹¹.

In relation to ACTH-independent Cushing's syndrome, 8 patients (18%) evidenced unilateral cortisol-producing adenomas, a very similar number to that reported in the literature, whose ranges lie between 10 and 27%^{4,8-11}; however, the literature includes in this case male-to-female distributions of 4-8:1⁴, inconsistent with the present study, where this pathology predominated in men but demonstrated no statistical significance. There were no cases of adrenal carcinoma, although it is specified in 5-7% of cases in the literature⁴.

Cushing's disease is related to multiple comorbidities, including cardiovascular, metabolic, musculoskeletal, kidney, psychiatric, and cognitive disorders¹⁵. In our study, the proportion of associated diseases is lower than that described in other series. Hypertension is one of the principal characteristic of endogenous Cushing syndrome, with a prevalence that ranges from 55 to 85%^{15,16}, dissimilar from our findings, where it affected only 47% of our subjects. Diabetes mellitus is often observed when the disease is newly diagnosed, with many diagnosis thereof made before recognizing Cushing's disease in the patient¹⁷. It has been reported that up to 70% of cases have impaired glucose metabolism¹⁸, with a prevalence of diabetes mellitus of between 20 and 47%¹⁵, compared with only 18% found in our study. The generally recognized prevalence of cardiovascular complications is between 23 and 62%¹⁵, with a presence of 22% in our series. It is unfortunate there are no reference data available for osteoporosis, myopathies, hirsutism, or menstrual irregularities to carry out a comparative study with our population.

Ki-67 protein is a marker for cell proliferation, but it does not evidence a correlation with the hormonal secretion grade of these lesions¹⁹. We found that the presence of Ki-67 was positive in 30 cases (67%), consistent with the available international literature, where approximately 52% of patients exhibited a Ki-67 > 1%¹⁹.

The response rates in our study to the established first-line treatment showed a remission rate after the initial surgery of 49%, lower than that described in other series, where it ranges from 69%²⁰ to 83%¹¹ and even reaches 90%²¹. The recurrence rate after the first surgery differs as well, our study exhibiting 32% rate thereof, compared to other publications where it ranges from 10% to 25%^{10-11,20-21}. In patients who underwent a second surgical intervention, general remission rates range from 50 to 70%^{19,21}, which are comparable to our results of 62%. The recognized recurrence rate after the second intervention is 9%²², very similar to our findings of 13%, and much < 50% relapse rate after the second intervention reported by Espinosa et al.²⁰

Pituitary surgical reintervention was the most often employed second-line treatment in our series for

those patients with recurring or persisting pathology. This is consistent with that described by Espinosa et al.²⁰ but contrasts with other series or reviews, where bilateral adrenalectomy and radiotherapy are considered the second-line treatment of preference²³.

With reference to ectopic tumors, our study found 69% remission rate, comparable to the findings described in the literature, where cure rates vary greatly, ranging from 12 to 71%, in view of the various tumor types that can be the culprits thereof²⁴.

Regarding medical treatment, medical literature supports ketoconazole as the most commonly prescribed medication for initial therapy²⁵; however, among those who continue to receive medications and suffered recurrence or persistence, the most commonly prescribed drug is pasireotide, which constitutes an analogue of multiple somatostatin receptors, and was the first medication approved by the European Medicines Agency indicated for patients with unsuccessful pituitary surgery²⁶, in such cases as those prescribed for our patients.

As of the date of this report, 78% of patients in our sample are in remission. However, the remission rate for the subgroup of patients with Cushing's disease is 71%. Conversely, 92% of patients with adrenal adenomas and ACTH-producing ectopic tumors had a long-lasting remission. These data must be carefully analyzed because the sample size for each is quite different. Consequently, a statistical analysis is not possible.

In light of the above mentioned, it must be noted that patient survival rates decrease as the number of treatments necessary to achieve remission increases; those cured with the first-line surgical intervention showed a mortality rate similar to that of the general population²⁷, which emphasizes the importance of having a highly experienced surgeon in this specialty carry out the procedure²⁸.

CONCLUSION

The efficacy of the various therapies available varies according to the populations studied; however, the

total remission rate for the disease is very similar to that described for the general international population. As this is a low prevalence disease, this type of studies allows us to recognize the particular behavior of this pathology at local level. Further studies are required to establish a national registry for this disease.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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