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Maite Cabrera Gámez *

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Research Article

Clinical Manifestations Before and After Surgical Treatment in Patients with Endogenous Hypercortisolism

Maite Cabrera Gámez[1], Emma Domínguez Alonso[1], Alina Acosta Cedeño[1], Silvia Elena Turcios[1]

National Institute of Endocrinology (INEN), University of Medical Sciences of Havana. Havana Cuba.

***Corresponding Author:** Maite Cabrera Gámez., National Institute of Endocrinology (INEN), University of Medical Sciences of Havana. Havana Cuba

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Abstract

Endogenous hypercortisolism (EH) presents varied and complex clinical manifestations (CM) but useful in follow-up. Objective to describe the CM in patients with HE before and after surgery. Material and Methods: Prospective study, cohort of 25 patients with HE, evaluated before and after surgical treatment. Medians and ranges of quantitative variables and frequency distributions of qualitative variables were determined. Cross tabulations of the presence (or not) of symptoms and signs before and after surgery were carried out, using the McNemar test, comparison of medians of quantitative variables before and after surgery using the Wilcoxon test. Results: Cushing's disease predominated (64%). The median age at diagnosis was 45 years and at the time of the study 46 years. Some symptoms that improved after surgery: fatigue (before 64% vs after 36%, p=0.039), weight gain (92% vs 44%, p=0.002), decreased concentration (64% vs 20%, p =0.001), menstrual disorders (76% vs 36% p=0.013). Signs were: bruising (72% vs 16%, p=0.000), moon face (80% vs 40%, p=0.006), buffalo hump (80% vs 48%, p=0.021), supraclavicular fat (68% vs. 40%, p=0.039). The medians of the variables decreased and the difference before and after treatment were statistically significant. Conclusions: In this cohort, all manifestations improved with weakened symptoms after surgical treatment, reaffirming the usefulness of the clinical method for early diagnosis and follow-up of HE.

Key words: endogenous hypercortisolism; symptoms; signs

Introduction:

Endogenous hypercortisolism (EH) is an endocrine disorder characterized by varied clinical symptoms, produced by prolonged exposure to excess glucocorticoids in tissues and by its adverse consequences; it is ideal to make an early diagnosis, which in many cases can become a real challenge [1-3]. The incidence depends on the population studied and has been estimated at 2 to 3 cases per million inhabitants per year [4-6]. HE or Cushing syndrome (CS) as it is also known, has different causes: dependent and independent of corticotropic hormone (ACTH). ACTH-dependent causes include: production of ACTH by pituitary tumors, also known as Cushing's disease (CD), 70%, by extrapituitary tumors, ectopic Cushing's syndrome, and less frequently corticotropin-producing tumors (CRH) [6]. A 15%, is the result of the increase in the autonomous production of cortisol by tumors (adenomas or carcinomas) or hyperplasia of the adrenal glands [6]. It has been seen to be more common in females with a ratio of 3-4:1 [7]. A retrospective study spanning 10 years, conducted in China and published in 2019 [8] reported a similar ratio of 3.6: [1] in women. HE can be a diverse and sometimes complex clinical picture and therefore difficult to diagnose; In a review, which included more than 5 series of patients with HE, carried out by Susmeeta T col [7]. and published in 2015, the most frequent clinical characteristics were described: obesity and weight gain, moon fascie, hirsutism, facial plethora, violaceous stretch marks, menstrual irregularities, neuropsychiatric alterations, muscle weakness, osteopenia, high blood pressure, glucose intolerance, hyperlipidemia and nephrolithiasis. In a study carried out at the Institute of Endocrinology of Havana, Cuba, in 2013, Moreno et al. 9 in patients with active disease prior to surgical treatment, found the most frequent clinical manifestations: weight gain (78%), irregularities menstrual disorders (46%), fatigue (46%), increased abdominal circumference (88%), moon fascia (84%) and hirsutism (70%). The confirmatory diagnosis is hormonal and is based on demonstrating elevated levels of cortisol more than once and with several diagnostic tests [3, 10,11], to move on to definitive treatment, which is surgical [6]. It is important to evaluate the effectiveness of the treatment from a clinical point of view and to know, in the context we are in, what clinical characteristics are modified and that help to monitor this disease and recover the psychological and biological well-being of the patients; which motivated us to present the results of the cohort of patients treated at our institution, with the aim of describing the clinical manifestations in patients with endogenous hypercortisolism before and after surgery.

Material and method

A descriptive, longitudinal and prospective study was carried out in patients treated at the Institute of Endocrinology (INEN), La Havana, Cuba, with a recent diagnosis of endogenous hypercortisolism, aged ≥ 20 and ≤ 60 years in the period between January 2017-January 2021.

The patients were evaluated (clinical and hormonal) before surgical treatment and six months after it; twenty-five patients were included taking into account the INEN statistics, according to the new cases admitted per year, which are approximately between 6-8 cases. This research was part of a project that included the assessment of the quality of life of these patients.

They were asked for consent to carry out the research, and they filled out the data collection form created for this research, which contained variables related to the interrogation, pre- and post-surgical physical examination.

Variables:

• Age: current age, reason, years old

• Sex: according to biological sex, nominal, female/male

• Personal pathological history: depending on the presence of any history mentioned in the interview, nominal, diabetes mellitus/ high blood pressure/ others,

• Family pathological history: presence of a family member with the history, nominally, diabetes mellitus/hypertension/others

• Age at diagnosis: years old when the disease was diagnosed, reason, years

• Time of evolution of HE: time in years from diagnosis to the present, reason, years

• Diagnosis of endogenous hypercortisolism: causes of HE, nominal, Cushing's disease/Cushing's syndrome,

• Current symptoms: they will be obtained according to what is referred to in the history of the current illness and through questioning, nominal, present/absent.

• Current signs: they will be obtained according to what is referred to in the history of the current illness and through the physical examination, nominal, present/absent.

• Body mass index (BMI): ordinal, underweight (less than 18.5 Kg/m2), normal weight (18.5 – 24.9 Kg/m2), overweight (25 – 29.9 Kg/m2), obesity (more than 30 Kg/m2).

• Waist circumference (WC): reason, normal for women (less than and equal to 88 cm) altered (greater than 88 cm)

Statistical analysis: Mean and standard deviation of the quantitative variables and frequency distributions (absolute numbers and percentages) of the qualitative variables were determined. Cross-tabulations of the presence (or absence) of symptoms and signs before and after surgery were carried out, using the Mc Nemar test to explore the statistical significance of the possible association. The medians of quantitative variables (clinical, hormonal) before and after surgery were compared using the Wilcoxon test. A statistically significant difference was considered when the p value was less than 0.05.

Ethical aspects: The research was approved by the INEN ethics committee. It did not put aspects of the patients' physical or mental health at risk. Informed consent was requested, participation was voluntary and the confidentiality and discretion of the data obtained was guaranteed.

Results

Graph 1 shows the distribution of patients according to the cause of endogenous hypercortisolism. 64% had Cushing's disease and in 36% the cause was an adrenal adenoma.

The average time from diagnosis to surgery was 1.09 years. 68% of them were cured from a biochemical point of view six months after treatment.

The median age at diagnosis of the disease was 45 years with a range between 19 and 58 years. The median age of the patients at the time of the study was 46 years with a range between 20 and 58 years.

In relation to the distribution of the patients according to age range at the diagnosis of HE and at the time of the study, the groups between 40 - 49 years and 50 -59 years predominated with 36% and 28% respectively, figures that were similar in the two age groups studied, followed by the 30–39-year-old group, but with 12%. In this series, a patient was diagnosed with the disease at the age of 19.

Regarding personal pathological history, 48% of the patients had two comorbidities, diabetes mellitus and arterial hypertension, followed by 24% who only had arterial hypertension, 16% of the sample had other comorbidities and the same percentage reported a history of health. The average number of years of patients with comorbidities was 1.9.

Table 1 shows the symptoms reported by patients before and six months after surgical treatment. All symptoms improved after surgery, decreasing their frequency of presentation. Those that presented statistically significant differences were: fatigue (before 64% vs after 36%, p=0.039), weight increase (before 92% vs after 44%, p=0.002), back pain (before 80% vs after 52%, p=0.039), decrease in concentration (before 64% vs after 20%, p=0.001), menstrual disorders (before 76% vs after 36% p=0.013), decreased libido (before 68% vs after 28%, p=0.002) and decreased memory (before 56% vs after 16%, p=0.002)

Table 2 shows the signs present before and after surgery. All signs also improved after surgical treatment, among those that were statistically significant were: bruising (before 72% vs after 16%, p=0.000), redness (before 92% vs after 44%, p=0.000), face full moon (before 80% vs after 40%, p=0.006), buffalo hump (before 80% vs after 48%, p=0.021), supraclavicular fat (before 68% vs after 40%, p=0.039), thin skin and hirsutism presented similar percentages (before 76% vs after 36%, p=0.002 and p= 0.006 respectively).

Table 3 shows the median of some quantitative variables before and after surgical treatment. All the medians of the variables studied decreased and the difference before and after surgical treatment was statistically significant, except for ACTH. Cortisol post inhibition with 2 mg of dexamethasone: median before 363 vs after 50, p= 0.000; waist circumference: median before 107 vs after 94, p= 0.003.

Discussion

The most common etiology of HE are corticotropin-producing pituitary adenomas, which represent up to 15% of pituitary tumors, with an incidence of 1.6 cases per million people [12]. They are more common in women and are the cause of HE. in more than 70% of cases, followed by ACTH-producing ectopic tumors and adrenal lesions [13]. A recent Chinese study from 2019 [14] found that Cushing's disease was invariably the most common cause of HE in the period studied and this frequency ranges between 56.0%- 73.0% [14]. This study coincides with the previous ones, with a similar frequency.

Although there are several treatment modalities for, HE, surgical treatment is the first line for most of its causes. However, not all patients are initially cured with this treatment and recurrence rates are high despite apparently being cured for some years; For example, up to 10% recurrence is reported for Cushing's disease [15].

In the Chinese study [14] that analyzed some epidemiological characteristics of the patients studied for 10 years, it was found that the most frequent age range for both the dependent and independent causes of ACTH was between 30-39 years, unlike the present study that both Age at diagnosis of the disease as at the time of the study was the 40s, followed by the 50s. HE appears more frequently in the fifth decade of life [4].

In the research presented, the majority of the patients were married and this coincides with the frequency in the study by Sawant et al [16] where twenty-two patients (63%) had similar marital status. There is also a coincidence in the number of widows, one in the previous study and two in ours.

In relation to the comorbidities associated with HE, from a physiopathological point of view it is explained that hypercortisolemia affects both the function of the beta cell of the pancreas and insulin sensitivity, age avanzada, la historia familiar de diabetes y los defectos en la secreción de insulina juegan un rol adicional en la aparición de esta enfermedad [17].

It is known that 18.5% to 64% of patients with HE have alterations in glucose metabolism while 20-47% have frank diabetes mellitus (DM) [18,19,20].

In the study by Zhou et al. [14] the most frequent comorbidities were HTN (71.2%) and DM (38.9%), both coinciding with this study.

Giordano et al [21] found that the prevalence of alterations in glucose metabolism and DM is significantly reduced after one year of remission in patients with Cushing's syndrome; this was not observed in patients with the disease. Colao et al [22]. reported 27% and 33% alterations in glucose metabolism and DM respectively in patients with Cushing's disease after 5 years of remission.

Regarding HTN, HE intervenes in its pathogenesis by increasing the activity of mineralcorticoids, vasoconstriction, the production of endothelin 1 and inhibiting vasodilation [23]. Glucocorticoids modulate the renin angiotensin aldosterone system and the regulation of the autonomic nervous system [23]. Pivonello et al [24]. state that if hypercortisolism is not controlled, the management of HBP in this type of patient is very difficult.

In the study by Lambert JK et al. 20 the prevalence of HTN in the HE was approximately 70%, in the present study the prevalence was lower (24%) but it was double the frequency when DM was associated.

Giordano et al 21 found a significant reduction in the prevalence of HBP one year after remission, but only in patients with HE due to adrenal causes. Likewise, Colao et al [22]. reported that both systolic and diastolic pressure remained elevated in patients with CD after 5 years in remission, compared with controls matched for age, sex and BMI.

Among the most frequent clinical manifestations is body pain that generates limitations in and makes daily living activities difficult, which negatively affects general QoL. Hormonal disturbances also have a negative impact on energy levels and most patients complain of body weakness or easy early fatigue. Most of them are affected by the impact of changes in their physical appearance that later result in a deterioration in social functioning [16]. In this study, pain and fatigue were frequent and although they decreased, they remained present after surgical treatment.

Weight gain is the most common clinical characteristic reported, and can reach up to 82% 18. Nishioka H 25 states that, although it is common, it is not definitive in patients with CD. In the present study this was also the most frequent clinical manifestation, and occurred in 90% of patients before surgery. The distribution of fat in the central region, in the cervical dorsum (buffalo hump) and the facial plethora are typical characteristics, but with low specificity, as demonstrated by another Cuban study that used a comparison group [26]. La adiposidad central presente en el HE excede el tejido celular subcutáneo predominando la grasa visceral; entre los mecanismos propuestos se encuentran la disminución de la activación de la proteína quinasa del AMP (AMPK) con un consecuente incremento en la expresión de la enzima que sintetiza ácidos grasos (lipidsynthesizing enzyme fatty acid synthase (FAS) [27].

Carluccio A et al [28]. found in their study that after remission, parameters such as weight, BMI, waist circumference and fat deposits improved compared to the active phase of the disease. In this study, all patients had abdominal obesity and the referred parameters also improved significantly. This specific fat distribution often resolves after normalization of cortisol levels and is an important finding in distinguishing CD from exogenous obesity [28].

Among other clinical manifestations, it is reported that menstrual irregularities have a frequency of 56% as a result of the suppression of the function of the hypothalamus-pituitary-ovarian axis by hypercortisolemia [29]. This occurs at different levels, in the hypothalamus it produces a decrease in synthesis and release of gonadotropin-releasing hormone (GNRH), at the level of the pituitary gland it exerts the same effect, but at the level of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and at the ovarian level it directly modulates steroidogenesis and gametogenesis [30]. In this study, menstrual disorders were also among the most frequent and improved considerably after surgical treatment.

A study [31] in patients after adrenalectomy (including 28% of CD patients) found that the median time to resolution of symptoms was at least seven months, with some symptoms such as acne taking a median of 17 months. to be resolved. In fact, not all patients perceived themselves to be completely recovered. In the research we present, all clinical manifestations decreased and the majority with statistical significance six months after surgical treatment.

In a cohort of 102 patients treated for CD, 92% of patients reached the criteria for biochemical cure, while only 80.4% perceived themselves to be in remission 28. In our sample, 65% were not hypercortisolic, of them 52% cured and 16% with adrenal insufficiency (HE is considered cured of HE).

Conclusions

In patients with HE in this cohort, all clinical manifestations improved considerably six months after surgical treatment, reaffirming the usefulness of the clinical method for early diagnosis and follow-up of people with this condition.

Authorship contribution

Maite Cabrera Gámez: Development of the protocol, the research idea and participated in each of the stages of the research. She reviewed and approved the final version of the document.
Emma Domínguez Alonso: she performed statistical processing. She reviewed and approved the final version of the document.
Alina Acosta Cedeño: participated in the analysis of the results. She reviewed and approved the final version of the document.
Silvia Elena Turcios Tristá: participated in the preparation of the discussion. She reviewed and approved the final version of the document.
Maydelin Mustelier González: primary data collection. She reviewed and approved the final version of the document.

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