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ORIGINAL ARTICLE

Corticotroph cell hyperplasia as a rare cause of ACTH-dependent Cushing syndrome

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KEYWORDS
Corticotroph cell hyperplasia;
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Abstract
Objective: Our aim was to characterise a cohort of patients with Cushing's disease (CD) who did not present pituitary adenoma in magnetic resonance imaging (MRI), needing a catheterisation of the inferior petrosal sinus (CIPS), and to study the pathological findings of the pituitary gland in these subjects after transsphenoidal surgery in order to establish the aetiology of CD. Furthermore, we evaluated possible differences in the features of the diagnosis between hyperplasia and adenoma.
Subjects and methods: We included 16 subjects. 17 CIPS were done. Hormonal parameters were measured using standard methods. A microscopic histochemical study following standard procedures and immunohistochemical analysis was performed. The diagnostic criteria for adenoma and hyperplasia were based on the WHO classification.
Results: One patient was excluded for presenting an ACTH-producing bronchial neuroendocrine tumour. The 15 subjects with CD have a positive CIPS test indicating hypophyseal ACTH production. After transsphenoidal surgery, 12 patients showed a microadenoma and three (20%) a corticotroph cell hyperplasia. We found four recurrences after the transsphenoidal surgery (26%), with a mean time for recurrence of 105 months. We found that recurrence was more frequent in subjects with hyperplasia, and in those subjects with lower right/left ACTH ratio.
Conclusion: Our study, which was focused on patients with CD with no pituitary adenoma detected by MRI and a positive CRH test after CIPS, has found that 20% showed corticotroph cell hyperplasia as the cause of CD. Right/left ACTH ratio after CIPS was useful to differentiate adenoma from hyperplasia. This finding may have important prognostic and treatment implications. More studies are necessary to confirm our result.

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PALABRAS CLAVE
Hiperplasia de células corticotropas;
Enfermedad de Cushing;
Síndrome de Cushing

Hiperplasia de células corticotropas como una causa rara de síndrome de Cushing ACTH dependiente

Resumen
Objetivo: Nuestro objetivo fue caracterizar una cohorte de pacientes con enfermedad de Cushing (EC) que no presentaban adenoma hipofisario en la resonancia magnética (RM), precisando cateterismo del seno petroso inferior (CSPI), y analizar los hallazgos patológicos de la glándula pituitaria en estos sujetos tras la cirugía transesfenoidal con el fin de establecer la etiología de la EC. Además, evaluamos las posibles diferencias en los hallazgos diagnósticos entre hiperplasia y adenoma.
Sujetos y métodos: Incluimos a 16 sujetos. Se realizaron 17 CSPI. Los parámetros hormonales se midieron utilizando métodos estándar. Se realizó un estudio histoquímico microscópico siguiendo procedimientos estándar y análisis inmunohistoquímico. Los criterios de diagnóstico de adenoma e hiperplasia se basaron en la clasificación de la OMS.
Resultados: Uno de los pacientes fue excluido por presentar un tumor neuroendocrino bronquial productor de ACTH. Los 15 sujetos restantes presentaron una prueba CSPI positiva que indica una producción de ACTH hipofisaria. Después de la cirugía transesfenoidal, 12 pacientes mostraron un microadenoma y 3 (20%) una hiperplasia de células de corticotropina. Hubo 4 recidivas (26%) tras la cirugía (tiempo medio de recidiva 105 meses). La recidiva fue más frecuente en los pacientes con hiperplasia y en aquellos con cociente derecha/izquierda de ACTH más bajo.
Conclusión: En nuestro estudio, centrado en pacientes con EC sin adenoma hipofisario detectado por RM y una prueba de CRH positiva tras CSPI, el 20% presentaba hiperplasia de células corticotropas como causa de EC. Además, el cociente de ACTH derecha/izquierda tras CSPI fue útil para diferenciar adenoma de hiperplasia. Este hallazgo puede tener importantes implicaciones tanto pronósticas como de tratamiento. Son necesarios más estudios para confirmar nuestros resultados.

Introduction

Cushing's disease (CD) is a rare disease (1–3 cases per million subjects year) with important consequences in terms of morbidity and mortality. It usually presents an insidious evolution with non-specific symptoms, that makes the early diagnosis difficult.[1–3] The optimisation of the screening diagnosis tests has increased early diagnosis[4] contributing to changing the traditional aetiologies of CD. Pituitary adenoma is the cause of 80% of ACTH dependent Cushing's syndrome (CS) and 15% is due to ectopic origin.[2,5] Nuclear magnetic resonance imaging of the hypothalamus and pituitary gland (MRIHH) with gadolinium is useful to identify pituitary adenomas. This procedure is the most sensitive and specific.[2,5] In the case that MRIHH does not localise the pituitary adenoma, a catheterisation of the inferior petrosal sinuses (CIPS) with CRH stimulation is usually performed to confirm excess autonomous ACTH production in the pituitary, before recommending transsphenoidal surgery with a curative intent.[6]

The rate of remission after surgery is about 80% when the adenoma is localised by MRIHH, with a recurrence of 15%. In contrast, when the adenoma is not detected by MRIHH, the remission rate is only about 60% in long follow up periods.[7] Furthermore, previous studies have shown a higher risk of recurrence when MRIHH is negative but there is a positivity in the CIPS test.[8–10]

Corticotroph cell hyperplasia is an exceptional cause of CD which has been described in some case reports in patients with confirmed pituitary origin of hypercortisolism after removing the pituitary mass showing the histological study hyperplasia of corticotrophin cells.[6,11,12] In addition, there is a matter of debate if corticotroph cell hyperplasia is or is not required as the initial step of CD.

Based on previous data, we hypothesise that in patients with confirmed pituitary ACTH production (positive CIPS test) but no detectable pituitary adenoma by NMRHH the possibility of finding corticotroph cell hyperplasia as a cause of CD should be higher than in other ACTH dependent CS cohorts. In this sense, some authors have tried to find specific characteristics which could be useful to differentiate hyperplasia from adenoma because many times the diagnosis of corticotroph hyperplasia is overlooked.[13]

In this sense, our aims were to characterise a cohort of patients with ACTH-dependent CS without a pituitary adenoma detected by MRIHH and subjected to a CIPS stimulation test with CRH and to study the pathological findings of the pituitary gland in those subjects after transsphenoidal surgery. Furthermore, we evaluated possible differences in the features of the diagnosis between hyperplasia and adenoma.

Subjects and methods

Subjects

We studied 16 subjects with ACTH dependent CS with no image of adenoma in the MRIHH. Pre-surgery, all of them had

a CIPS stimulation test with CRH to demonstrate pituitary origin of ACTH overproduction. The subjects were consecutively recruited from our outpatient clinic.

All the patients studied attended our Endocrinology Unit at the Hospital Clinico Universitario of Valencia [Valencia Clinical University Hospital] in the period from 1992 to 2014 and signed an informed consent approved by the Ethics Committee of our centre. The CIPS tests were carried out in the Interventional Radiology Unit form our centre by the same group of radiologists. All of them were performed from 1992 to 2013. The same neurosurgical team (two skilled neurosurgeons) performed the interventions from 1992 to 2014.

One subject was excluded from the study, because the CIPS tests showed that it was not a CD and additional studies indicated an ectopic production of ACTH (bronchial carcinoid). After tumour removal, the patient maintained remission criteria for a four-year follow-up period.

In 15 subjects the CIPS test confirmed that the cause of CD was of hypophyseal origin. All of them were treated with transsphenoidal surgery. When the neurosurgeon detected a microscopic lesion, enucleation was performed. In the cases where no microlesions were found a hemihypophysectomy was done, guided by the result of the right/left plasma ACTH gradient after maximum stimulation with CRH. After surgery, the removed tissue was analysed in the Pathological Anatomy Service of our Centre for cell characterisation and immunohistochemistry was performed (see below).

Inclusion criteria

The inclusion criteria were: man or woman, aged from 18 to 70 years, ACTH-dependent CS and negative MRIHH for adenoma, CIPS: baseline plasma ACTH central to peripheral gradient ≥ 2 or after maximum stimulation plasma ACTH central to peripheral gradient ≥ 3, transsphenoidal surgery and histopathological characterisation after the surgery.

ACTH-dependent CS was diagnosed if the patient fulfilled the four following criteria: (1) Cortisoluria more than three times the upper normal value (in our laboratory > 150 μg/24 h); (2) Two days suppression test with 0.5 mg of dexamethasone every 6 h: 9.00 am cortisol value ≥ 2 μg/dl; (3) Overnight 1 mg dexamethasone suppression test at 23 h: 9.00 am cortisol value ≥ 2 μg/dl; and (4) 9.00 am ACTH value ≥ 20 pg/ml.

Exclusion criteria

The exclusion criteria were: ACTH-independent Cushing Syndrome (9.00 am ACTH value ≤ 10 pg/ml), ACTH dependent Cushing's syndrome with MRIHH that showed pituitary adenoma, no surgery and/or histological studies.

Remission and recurrence criteria

We considered remission criteria to be when 9.00 am cortisol value (last taking prednisone as replacement therapy at 9.00 am on the day before) < 5 μg/dl at 14 days after the intervention or 9.00 am cortisol value < 1.8 μg/dl at three months after surgery.[14,15]

The recurrence criteria were absence of remission criteria and abnormal overnight 1 mg dexamethasone suppression test: 9.00 am cortisol value ≥ 2 μg/dl.

All the subjects were followed up after surgery at 14 days, 3, 6 and 12 months. Subsequently an annual follow up with measurement at 9.00 am of cortisol, cortisoluria and the performance of an overnight 1 mg dexamethasone suppression test was performed, if the patient maintained remission criteria.

Methods

Clinical

Clinical parameters were collected by clinical interview: age, gender and personal history (hyperglycaemia, hypertension, obesity, depression and osteoporosis; and non-related to CS, such as surgical background and other disease).

Anthropometric parameters as height, weight, waist circumference and body mass index were measured by standardised methods.

Hormonal values

Plasma cortisol was measured by chemiluminescent competitive immunoassay with the Analyzer Cobas 8000 (Roche Diagnostics, Rotkreuz, Switzerland), considering normal as 5–25 μg/dl at 9.00 am. Plasma ACTH was measured using ELISA with the Analyzer Cobas 8000 (Roche Diagnostics, Rotkreuz, Switzerland), considering normal as 5–60 pg/ml. Urinary cortisol was determined using the competitive chemiluminescent Analyzer (Siemens) Architect immunoassay technique.

Two days suppression test with 0.5 mg of dexamethasone consisted in the administration of 0.5 mg of dexamethasone orally every 6 h for 2 days and measurement of cortisol at 9.00 am the next day.

The overnight 1 mg dexamethasone suppression test consisted in the administration of 1 mg of dexamethasone at 11.00 pm and measurement of cortisol at 9.00 am the next day.

Two days suppression test with 2 mg of dexamethasone consisted in the administration of 2 mg of dexamethasone every 6 h orally for two days and measurement of cortisol at 9.00 am the next day.

Magnetic resonance imaging (MRI)

The MRIHH was performed with the administration of gadolinium in the Radiology Service of our centre. High-resolution, contrast-enhanced and thin-section MRI scans were done. Cuts of less than a millimetre were done to detect microadenomas. This test was interpreted by two expert radiologists dedicated to endocrine image analysis in our centre.

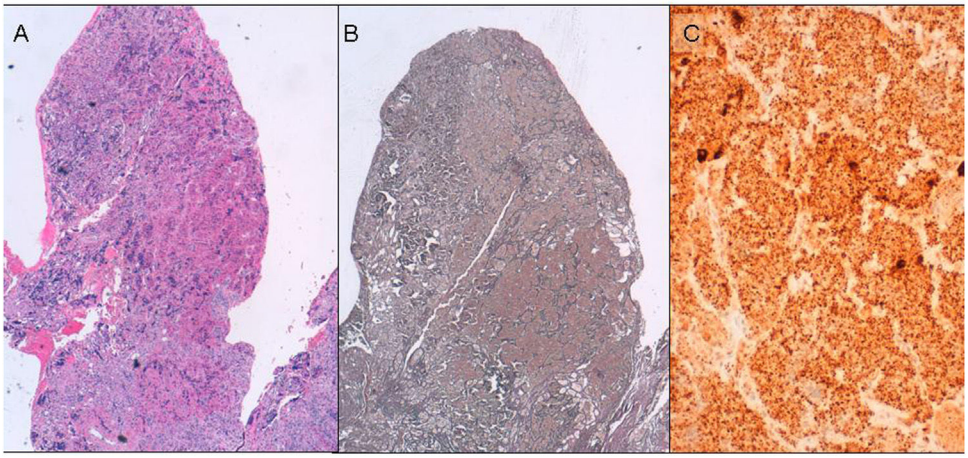

Figure 1 Photomicrographs of samples of corticotroph hyperplasia. (A) H.E stain, 4×. Expanded acini with homogenous eosinophilic cells. (B) Expanded reticulin network, 4×. (C) ACTH immunostaining, 40×. H.E: haematoxilin–eosin.

Catheterisation of inferior petrosal sinuses (CIPS)

Catheterisation was performed by two experienced radiologists at our centre after 8 hours' fasting. We used local anaesthesia in order to perceive presentation of problems like otalgia during the procedure.

A peripheral vein was catheterised in one arm to collect samples of peripheral blood. Catheterisation of the femoral veins with two 5F introducers was done. For each introducer, we passed a 5F catheter to reach inferior petrosal sinus. The procedure was performed under fluoroscopic control. To check the correct position of the catheter, a small amount of iodinated contrast was inserted. To obtain detailed information about the procedure see reference.[16]

After correct catheterisation, CRH was administered (1 μg/kg). ACTH was measured at − 5, baseline (0) and 2, 3, 5, 10 min after the administration of CRH.

Histopathological study

We performed a microscopic study from formalin-fixed, paraffin-embedded specimens. In each case a routine H.E. staining, reticulin histochemical study following standard procedures and immunohistochemical analysis were performed[17] (Fig. 1).

Samples were sectioned for immunostaining sections, processed by Envision Flex (Dako) and stained with antibodies to ACTH (Dako; 1/200), prolactin, (Novocastra; 1/400), TSH (Dako; prediluted), HGH (Dako; 1/1000), FSH (Dako; 1/50), LH (Dako1/100) and Ki67 (Dako; prediluted). Antigenic retrieval was performed with PT-Link, and low pH buffer. We detected antibody binding with DAB as the chromogen.

The diagnostic criteria for adenoma and hyperplasia were based on the WHO classification.[18] In summary: the architectural pattern in acini for normal tissue, expanded acini for hyperplasia and nodular pattern for adenoma. The reticulin network is essential in differential diagnosis. It is surrounding the acini in normal tissue, expanded in hyperplasia and lost in adenoma. Finally, cells are monomorphous in both pathological cases and heteromorphous in normal tissue.

Statistical methods

Data were analysed using the Statistical Package for the Social Sciences (SPSS 12.1.3 for Windows; SPSS Chicago, IL, USA). Quantitative variables are expressed as mean and standard deviation. The qualitative variables are expressed in total number or percentage.

The comparative analysis of the variables was made using the Mann–Whitney test. Qualitative variables were analysed using the Chi square test. We considered a p value below 0.05 to be statistically significant.

Results

We studied 16 individuals. One of them was excluded because CS was due to a bronchial carcinoid tumour producing ACTH. Finally, we included 15 individuals (11 women and 4 men) in the study. All of them presented CD with no adenoma localised by high-resolution, contrast-enhanced and thin-section MRIHH. In the 15 subjects a CIPS stimulation test with CRH was performed prior to surgery. In all of them, the test showed a pituitary origin of CD. We show the clinical and biological characteristics of the studied patients in Tables 1 and 2, including data about lateralisation (except for patient 8 for whom it was not possible to evaluate both sides).

After transsphenoidal surgery, 12 patients (80%) showed a microadenoma and three (20%) a corticotroph cell hyperplasia (Table 2). During the follow-up period (1992–2015) four recurrences out of 15 patients (26%) were observed. The mean time for recurrence was 105 months (more than eight years). In Table 3 we show the clinical and hormonal parameters classifying the studied subjects as still being in remission or not. We found that recurrence was more frequent in subjects with hyperplasia, and in those subjects with lower right/left ACTH ratio.

The patients who presented recurrence remain currently in remission after a minimum follow-up period of 18 months (radiotherapy or a new surgery was needed). Unfortunately, 12 patients had panhypopituitarism and three

Table 1 Clinical characteristics and hormonal values of patients with ACTH dependent Cushing syndrome with no adenoma detected by MRIHH and studied with CIPS.

$n = 15$	Average ± standard deviation
Age (years)	38.1 ± 7.9
BMI (kg/m^2)	27.5 ± 3.6
Cortisoluria (mg/24 h)	653.1 ± 509.4
9.00 am Cortisol (μg/dl)	31.9 ± 12.6
9.00 am ACTH (pg/dl)	75.3 ± 57.7
Cortisol 9.00 am after two days suppression test with 0.5 mg of dexamethasone every 6 h (μg/dl)	21.2 ± 9.8
Cortisol 9.00 am after two days suppression test with 2 mg of dexamethasone every 6 h (μg/dl)	13.5 ± 10.4
Catheterisation follow up (years)	10.1 ± 6.5
Central ACTH (pg/dl)	506.1 ± 646.4
Peripheral ACTH (pg/dl)	71.7 ± 67.6
Central/peripheral baseline ACTH ratio	9.4 ± 10.7
Peripheral ACTH after CRH stimulation (pg/dl)	110.7 ± 122.0
Central ACTH after CRH stimulation (pg/dl)	1874.6 ± 1493.1
Central/peripheral ACTH ratio after CRH	43.3 ± 37.1
ACTH ratio after CRH (lateralisation)	7.3 ± 6.1
Follow up after surgery (years)	9.7 ± 6.3

BMI: body mass index; MRIHH: magnetic resonance imaging of the hypothalamus and hypophysis; CIPS: catheterisation of inferior petrosal sinus.

Table 2 Characteristics of the patients with ACTH dependent Cushing syndrome.

Case no.	Age (years)	Gender	Right ACTH (pg/dl)	Left ACTH (pg/dl)	Right/left ACTH ratio	Remission	Histological diagnosis
1	48	Male	1369	1794	1.3	Yes	Left adenoma
2	41	Male	648	61	10.6	No	Right adenoma
3	33	Female	1908	1307	1.4	No	Hyperplasia
4	39	Female	221	1797	8.1	Yes	Left adenoma
5	23	Male	1237	59.8	20.6	Yes	Right adenoma
6	41	Male	246	5143	20.9	Yes	Left adenoma
7	45	Female	770	55	14	Yes	Right adenoma
8	46	Female	NA	NA	NA	No	Hyperplasia (right adenoma after second surgery)
9	46	Female	689	4425	6.4	Yes	Left adenoma
10	28	Female	2172	33	65.8	Yes	Right adenoma
11	38	Female	18.2	4.4	4.55	Yes	Right adenoma
12	40	Female	436	1816	4.1	Yes	Left adenoma
13	23	Female	2351	642	3.6	Yes	Right adenoma
14	41	Female	1973	183	10.7	Yes	Right adenoma
15	40	Female	1227	2001	1.63	No	Hyperplasia

Right/Left ratio was calculated dividing the highest value by the lowest.
NA: not available.

partial hypopituitarism (three subjects hypogonadism and one hypothyroidism).

Finally, we also evaluated the characteristics of subjects with adenoma and hyperplasia (Table 4). We found that those patients with diagnosis of adenoma showed higher baseline ACTH levels and higher right/left ACTH ratio during CIPS.

Discussion

We found four recurrences from 15 CD studied (26%), after transsphenoidal surgery. A similar recurrence rate was found in other studies. In addition, in patients with no adenoma detected by MRIHH, treated with hemihypophysectomy, the remission rate is about 50%.[19] Moreover, when the follow up

Table 3 Clinical and hormonal values of patients with ACTH dependent Cushing syndrome classified depending on recurrence.

	Dependent ACTH CS in remission ($n = 11$)	Dependent ACTH CS with recurrence ($n = 4$)	p
Age (years)	38.4 ± 8.8	37.5 ± 6.3	0.512
BMI (kg/m^2)	26.5 ± 2.98	29.3 ± 4.5	0.920
Cortisoluria (μg/24 h)	759.3 ± 597.8	849.2 ± 334.2	0.712
Baseline Cortisol (μg/dl)	32.1 ± 13.11	29.9 ± 8.43	0.599
Baseline ACTH (pg/dl)	79.2 ± 70.19	70.3 ± 35.22	0.174
Cortisol after two days suppression test with 0.5 mg of dexamethasone every 6 h (μg/dl)	21.9 ± 7.1	18.6 ± 9.3	0.143
CIPS (years)	10.3 ± 4.8	14.8 ± 6.2	0.619
Central ACTH at baseline (pg/dl)	415.8 ± 579.4	350.3 ± 470.7	0.229
Peripheral ACTH at baseline (pg/dl)	78.5 ± 80.45	53.0 ± 43.5	0.146
Central ACTH after maximal stimulus with CRH (pg/dl)	1556.7 ± 1490.6	1914.2 ± 2274.0	0.512
Central/peripheral baseline ACTH ratio	8.6 ± 12.2	7.3 ± 9.0	0.954
Central/peripheral ACTH ratio after CRH stimulation	40.6 ± 39.2	31.8 ± 29.6	0.508
Right/left ACTH ratio after CRH stimulation	8.8 ± 6.1	2.21 ± 1.3*	0.012
Time from surgery (years)	10.0 ± 4.9	14.0 ± 6.1	0.669
Time free of recurrence (months)	–	105.0 ± 100.6	–
Adenoma/hyperplasia	11/0	1/3*	0.011

BMI: body mass index; CIPS: catheterisation of inferior petrosal sinus; CS: Cushing syndrome.
* Statistically significant.

Table 4 Clinical and hormonal values of patients with ACTH dependent Cushing syndrome classified depending on histological diagnosis after surgery.

	Patients with corticotroph adenoma ($n = 12$)	Patients with corticotroph hyperplasia ($n = 3$)	p
Age (years)	39.2 ± 8.2	33.7 ± 6.0	0.168
BMI (kg/m^2)	27.8 ± 3.6	26.4 ± 2.7	0.306
Cortisoluria (μg/24 h)	682.5 ± 555.1	357.5 ± 234.9	0.484
Baseline Cortisol (μg/dl)	32.7 ± 14.2	28.9 ± 0.9	0.664
Baseline ACTH (pg/dl)	87.2 ± 60.0	31.7 ± 3.9*	0.016
Cortisol after two days suppression test with 0.5 mg of dexamethasone every 6 h (μg/dl)	23.8 ± 9.8	13.3 ± 5.1	0.052
CIPS (years)	10.7 ± 6.4	7.7 ± 7.6	0.633
Central ACTH at baseline (pg/dl)	560.1 ± 717.2	307.8 ± 262.2	0.938
Peripheral ACTH at baseline (pg/dl)	82.9 ± 72.2	30.4 ± 20.5	0.186
Central ACTH after maximal stimulus with CRH (pg/dl)	2041.2 ± 1603.1	1319.3 ± 1100.2	0.800
Central/peripheral baseline ACTH ratio	9.2 ± 11.3	10.3 ± 8.9	0.697
Central/peripheral ACTH ratio after CRH stimulation	41.4 ± 33.5	49.7 ± 55.6	0.842
Right/left ACTH ratio after CRH stimulation	8.9 ± 5.9	1.5 ± 0.9*	0.036
Time from surgery (years)	10.5 ± 6.3	6.7 ± 6.6	0.383
Time free of recurrence (months)	69.5 ± 81.6	64 ± 70.3	0.891

BMI: body mass index; CIPS: catheterisation of inferior petrosal sinus.
* Statistically significant.

period is longer (more than 10 years) the rate of recurrences increased to 26% in subjects with detectable adenoma by MRIHH.[7,17]

In our cohort, three patients showed corticotroph cell hyperplasia as the pathological finding, which represents 20% of the total number of studied cases. This result confirmed our hypothesis. It is remarkable that all the patients with hyperplasia had recurrence. However, only one out of 12 (8.3%) with diagnosis of adenoma presented recurrence (Table 3). When we analysed the factors which could be related to recurrence, we found that those patients with diagnosis of adenoma showed higher baseline ACTH levels and higher right/left ACTH ratio during the CIPS test (Table 4). In fact, subjects with hyperplasia presented weak lateralisation or it was even absent. Although more studies are necessary, a CIPS test could be useful to anticipate the diagnosis of hyperplasia. Furthermore, the CIPS test was able to guide the neurosurgical procedure.

The neurosurgeon performed an exploration of the pituitary gland, mainly guided by the presence of lateralisation after the administration of CRH. In those cases, in which an adenoma was observed, it was enucleated. In cases in which no type of lesion was evident, hemihypophysectomy was performed based on previous CIPS test lateralisation. The concordance between the CIPS test and the location of the lesion was very high (Table 2).

There are few data about the parameters associated to recurrence. Ciric et al.[10] showed that peripheral to central ACTH gradient at baseline or after maximum stimulation with CRH was associated with a high incidence of hormone remission in the immediate postoperative period. However, in this study all CD patients presented adenoma in the MRIHH.[10] Therefore, the results observed by Ciric et al. are not comparable with those found in the present study, in which only CD patients with no adenoma in MRIHH were included.

Catalino et al. also evaluated diagnostic features, surgical management, and clinical outcomes to compare corticotroph hyperplasia and histopathologically proven adenomas in patients with Cushing disease. However, no specific findings were obtained.[13]

In other studies, corticotrophin cell hyperplasia has been described as responsible for ACTH-dependent CS in some case reports.[6,11,12] In addition, hyperplasia with transformation to adenoma has been described as a rare cause of CD[20,21] and hyperplasia and adenomas have been found in the sample of the same patient with CD.[22] It is note that one of our four patients who experienced recurrence showed a corticotroph cell hyperplasia but in the second surgery a microadenoma as the pathological finding was established (Table 2; patient 8).

However, not all the authors agree with the definition of corticotroph cell hyperplasia. We have used diagnostic criteria based on the WHO recommendations.[18] In addition, the three patients with corticotroph cell hyperplasia showed remission criteria after surgery suggesting that this pathological finding was the cause of CD. None of them presented persistent disease after surgery.

Our study has some limitations. The sample size is small, although it is representative. In fact, Nishioka et al.[9] studied a cohort of 124 patients with ACTH-dependent CS. Only 18 had a negative MRIHH. In addition, the diagnostic criteria of CS have experienced some changes during the time of the study. Even this, our study is original. We have included only patients with no adenoma detected by MRIHH with a median follow-up period of 8 years. In addition, the CIPS test, MRIHH interpretation and pathological studies have been made by the same group of researchers.

In conclusion, the present cohort focused on patients with ACTH-dependent CS with no pituitary adenoma detected by MRIHH and a positive CIPS test after CRH, and 20% of the patients showed a corticotroph cell hyperplasia as the cause of CD. Furthermore, the CIPS test guided surgery in an efficient way, and could be useful to differentiate adenoma and hyperplasia. Nevertheless, multi-centre studies involving a greater number of subjects with ACTH-dependent CS with no adenoma detected by MRIHH are necessary to know the real prevalence of corticotroph cell hyperplasia as the cause of CD. In addition, these studies could identify biological and/or hormonal predictors of hyperplasia diagnosis and recurrence in this subgroup of patients where the rate of recurrences is very high.

Conflict of interest

The authors declare that they have no conflict of interest.

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