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BRIEF COMMUNICATION

Adrenocorticotropic Hormone-Dependent Cushing's Syndrome

Use of an octreotide trial to distinguish between pituitary or ectopic sources

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مرض كوشنج بسبب زيادة إفراز الهرمون الموجِّه لقشر الكظر

استعمال أوكتريوتايد لمعرفة مصدر زيادة إفراز الهرمون الموجِّه لقشر الكظر من الغدة النخامية أم من خارجها

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ABSTRACT: ***Objectives:*** Adrenocorticotropic hormone (ACTH) overproduction is usually due to a pituitary tumour which is often not visible on magnetic resonance imaging (MRI). However, ACTH overproduction may be due to an ectopic source. This study aimed to develop a simple non-invasive technique to differentiate these sources. ***Methods:*** This study took place in King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, and Sultan Qaboos University Hospital, Muscat, Oman, between 1988 and 2012. Serum cortisol levels were measured in nine patients with ACTH-dependent Cushing's syndrome before and during a 72-hour trial of octreotide. All patients underwent computed tomography (CT) scans. MRI scans were performed on six patients. ***Results:*** CT scans were abnormal in three patients with ectopic ACTH production. MRI scans showed that three patients had pituitary microadenomas. Serum cortisol levels returned to normal in those with confirmed ectopic ACTH production. No response was found in the other six patients. ***Conclusion:*** A 72-hour trial of octreotide is recommended for patients with ACTH-dependent Cushing's syndrome and a normal pituitary MRI. This trial will be a useful alternative to petrosal sinus sampling.

Keywords: Adrenocorticotrophic Hormone; Cushing's Syndrome; Somatostatin Receptors; Investigational Therapies; Octreotide; Saudi Arabia; Oman.

الملخص: الهدف: إن زيادة إفراز الهرمون الموجِّه لقشر الكظر (ACTH) المسبب لمرض كوشنج غالبا ما يكون بسبب ورم صغير في الغدة النخامية وفي معظم الأحيان لا يمكن تحديد الوَرم بأشعة الرنين المغناطيسي، كما أن إفراز هذا الهرمون قد يكون بسبب ورم خارج الغدة النخامية. الغرض من هذه الدراسة هو توضيح طريقة بسيطة يتم من خلالها معرفة مصدر الزيادة في إفراز هرمون(ACTH) ما إذا كان من الغدة النخامية أو مكان آخر في الجسم. **الطريقة:** تمت هذه الدراسة في مستشفى الملك فيصل التخصصي ومركز الأبحاث، الرياض، المملكة العربية السعودية، ومستشفى جامعة السلطان قابوس، مسقط، سلطنة عمان، بين عامي 1988 و 2102م. تمت الدراسة على تسع مرضى يعانون من مرض كوشنج بسبب زيادة إفراز هرمون اي.سي.تي.ايج حيث قمنا بمراقبة مستوى هرمون الكورتيزول في الدم قبل وخلال 72 ساعة من بدء العلاج بالاوكتريوتايد. تم أخذ أشعة مقطعية لجميع المرضى التسعة و أجري فحص الرنين المغناطيسي على ستة مرضى. **النتائج:** كانت نتائج الأشعة المقطعية غير طبيعية في ثلاثة من المرضى الذين كانوا مصابين بأورام خارج الغدة النخامية. أظهرت نتائج الرنين المغناطيسي أن ثلاثة من المرضى لديهم ورم صغير في الغدة النخامية. انخفض مستوى هرمون الكورتزول إلى الطبيعي عند المرضى الذين كانوا مصابين بأورام خارج الغدة النخامية أما المرضى الستة الباقين فإن مستوى الكورتزول بقي مرتفعا. **الخلاصة:** ننصح باستعمال الاوكتريوتايد لمدة 72 ساعة مع كل مرضى كوشنج بسبب زيادة إفراز هرمون اي.سي.تي.ايج والذين تكون نتيجة الرنين المغناطيسي للغدة النخامية طبيعية لديهم، كما أنه يمكن استعمال هذه الطريقة للتشخيص كبديل عن قياس هرمون (ACTH) عن طريق سحب عينات الدم من داخل أوردة الجمجمة.

مفتاح الكلمات: الهرمون الموجِّه لقشر الكظر؛ مرض كوشنج؛ مستقبلات سوماتوستاتين؛ العلاجات البحثية؛ الأوكتريوتايد؛ المملكة العربية السعودية؛ سلطنة عمان.

The most common cause of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome is a pituitary adenoma (90%).[1] When this cause is identified, the condition is also known as Cushing's disease. Other cases of ACTH-dependent Cushing's syndrome are due to ectopic ACTH secretion, generally by bronchial or pancreatic neuroendocrine tumours (NETs) or, rarely, tumours that secrete corticotropin-releasing hormone (CRH).[2] However, in 40% of patients with Cushing's disease, magnetic resonance imaging (MRI) shows a normal pituitary gland.[3] These patients must be distinguished from those with ectopic ACTH production. The gold-standard practice for differentiating pituitary from ectopic ACTH overproduction is performing inferior petrosal sinus sampling (IPSS) with serial ACTH measurements after the intravenous administration of CRH. This procedure

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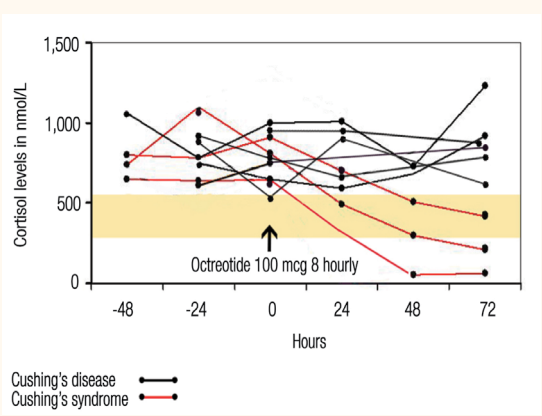

Figure 1: Serum cortisol levels in nine patients with adrenocorticotropic hormone-dependent Cushing's syndrome before and during a trial of octreotide. Only three patients, all of whom were found to have neuroendocrine tumours, responded to treatment.

Grey bar = normal cortisol levels.

necessitates the cannulation of both jugular veins and is therefore invasive and costly.[4] As a result, the Sultan Qaboos University Hospital (SQUH), a tertiary centre in Muscat, Oman, relies on indirect testing to confirm or refute the pituitary source. As most NETs express somatostatin receptors type 2 and 3, they are therefore amenable to treatment with octreotide which lowers ACTH and cortisol levels.[5–7] Patients with Cushing's disease do not respond to octreotide due to the lack of expression or downregulation of somatostatin receptors.[8] Furthermore, patients with NETs secrete chromogranin A (Cg-A) as well; it has therefore been theorised that the measurement of Cg-A levels may prove to be of additional diagnostic value.[9] In light of these factors, and because IPSS is not available in all centres, the objective of this study was to test the use of a 72-hour trial of octreotide to distinguish between pituitary and ectopic ACTH overprodu ction.

Methods

This study took place in King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, and SQUH between 1988 and 2012. Nine patients with ACTH-dependent Cushing's syndrome confirmed by elevated fasting serum cortisol and ACTH levels were included in the study. Four of these patients have previously been reported in the literature.[5] Computed tomography (CT) scans of the neck, chest and abdomen were carried out on all patients. In addition, six patients underwent MRI scans and two had their Cg-A levels measured on admission after fasting. Each patient undertook a 72-hour therapeutic trial of octreotide, with a dose of 100 mcg administered every eight hours. Serial cortisol measurements were taken at the beginning of the trial (8 am) and then subsequently 24, 48 and 72 hours after the trial had begun. Some patients had basal samples taken 48 and 24 hours before the trial began.

Subjects whose serum cortisol levels were unchanged throughout the study period were determined not to have responded to the octreotide trial, while patients whose serum cortisol levels decreased to within a normal range were determined to have responded to the treatment. All patients and their families gave consent for their inclusion in the study.

Results

A total of nine patients with ACTH-dependent Cushing's syndrome were identified during the study period. Serum cortisol levels were unchanged in six patients but fell progressively to normal levels in the remaining three patients [Figure 1]. The six subjects who did not respond to the octreotide trial had normal CT results of the neck, chest and abdomen. In comparison, the patients who responded to the treatment had abnormal CT scans of the lung and pancreas. Cg-A levels were normal in the two patients who did not respond. Of the six patients who did not respond to the octreotide, MRI scans revealed pituitary microadenomas in three, while the other three patients had normal MRI results.

Among the three subjects who responded to octreotide, NETs were identified as the source of the ACTH overproduction. Before the trial started, one of the three patients was documented to have a benign bronchial carcinoid tumour while the other two were identified as having metastatic pancreatic NETs producing ACTH both radiologically and histologically. The first patient had no need for further treatment following the removal of the benign bronchial carcinoid tumour. The other two patients died within a year of diagnosis.

For the six patients who did not respond to octeotride, pituitary adenomas (Cushing's disease) were identified as the source of the ACTH over-production. Of these, five underwent transsphenoidal surgeries (TSS) [Table 1]. Two patients were cured after their surgeries, while another two relapsed initially but at the time of writing were both in complete remission and receiving cabergoline treatment. One patient relapsed and received external radiotherapy; after this, the patient went abroad and was lost to follow up. At the time of writing, the final patient was in complete remission and was receiving cabergoline therapy without any other interventions.

Table 1: Fasting serum cortisol and ACTH levels and imaging results in nine patients with ACTH-induced Cushing's syndrome at presentation and subsequently identified source of ACTH overproduction

Patient	Cortisol levels in nmol/L*	ACTH levels in pmol/L**	CT/MRI	TSS	Source
1	675	25	-	-	Ectopic (lung carcinoid)
2	826	9	-	-	Ectopic (pancreatic carcinoid)
3	856	27	-	-	Ectopic (pancreatic carcinoid)
4	612	13	Normal	Performed	Pituitary
5	812	4	Normal	Performed	Pituitary
6	752	14	Normal	Not perfomed	Pituitary
7	923	24	Microadenoma	Perfomed	Pituitary
8	700	16	Microadenoma	Performed	Pituitary
9	1,100	6	Microadenoma	Performed	Pituitary

*ACTH = adrenocorticotropic hormone; Cg-A = chromogranin A; CT = computed tomography; MRI = magnetic resonance imaging; TSS = transsphenoidal surgery. *Normal range: 184–580 nmol/L; **Normal range: 1.6–13.9 pmol/L.*

Discussion

ACTH-dependent Cushing's syndrome is rare and usually caused by a pituitary adenoma; however, 10% of cases are ectopic.[1,2] If the source of the ACTH overproduction is not readily apparent, centres with the necessary resources can carry out IPSS with ACTH measurements. This procedure will distinguish pituitary from ectopic sources and help localise the site of the tumour within the pituitary gland. However, as IPSS is not yet available in all centres, it is important to develop alternative approaches. One such approach consists of a short trial of octreotide, which has been assessed and reported previously.[5] As shown in the current study, only three patients with ACTH-dependent Cushing's syndrome were found to have decreased cortisol levels and therefore to have responded to the octreotide treatment; these patients were subsequently found to have NETs. In comparison, there was no response in the remaining six patients who were diagnosed with Cushing's disease.

Somatostatin receptors are expressed in normal pituitary ACTH-producing cells; however, it has been found that the expression of somatostatin receptors 2 and 3 is downregulated by elevated glucocorticoid levels.[8] This explains why octreotide is not therapeutically useful in Cushing's disease. A study by de Herder *et al*. using somatostatin receptor imaging further supports the results of the present study, as octreotide scanning was negative in eight patients with ACTH-secreting pituitary adenomas whereas uptake was positive in all 10 of their patients identified with NETs producing ectopic ACTH.[9]

Most NETs co-secrete Cg-A with hormones;[10] thus, the measurement of circulating Cg-A levels was recently added to the octreotide trial procedure reported in the current study. This measurement was included as a further diagnostic tool to distinguish pituitary from ectopic disease. This combination is currently carried out routinely in SQUH.

In another recent study conducted in Oman, high-dose cabergoline was used successfully to treat four patients with Cushing's disease.[11] Although one of the patients refused surgery, they were treated with cabergoline monotherapy; the dosage was reduced from 1 mg/day to 1 mg twice weekly and the patient has remained in complete remission for almost three years since the time of writing.[11] As a result of these observations, the current practice at SQUH is to offer a short-term trial of cabergoline to patients with ACTH-dependent Cushing's syndrome who do not respond to octreotide and have normal pituitary MRIs. If the patient responds, they may be offered long-term cabergoline treatment or a laparoscopic adrenalectomy. Should the patient subsequently develop Nelson's syndrome, a TSS may then be carried out.[12]

Conclusion

The results of this study indicate that a 72-hour trial of octreotide is advisable for all patients with ACTH-dependent Cushing's syndrome and normal MRI results. This procedure has been shown to be a safe and simple method that will effectively distinguish between pituitary and ectopic ACTH overproduction. In addition, it is a useful alternative to IPSS in centres where this procedure is not available.

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