

Cushing's Disease

Pituitary Surgery versus Adrenalectomy

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مرض كوشينغ

جراحة الغدة النخامية مقابل استئصال الغدة الكظرية

اميمة الشفيق، فاطمة بن عبد، نايل الكندي، ديليب شنكل، نيكولاس وودهاوز

الملخص: هذا وصف حالتين لمرض كوشينغ من قسم الطب الباطني بمستشفى جامعة السلطان قابوس في سلطنة عمان. كان سبب المرض وجود ورم صغير جدا بالغدة النخامية. ونظرا لصغر حجم الورم بالغدة النخامية لم تستطع صور الرنين المغناطيسي من اكتشافه. المريض الأول (بلغ من العمر 14)) عاما وكان يعاني من هذا المرض لعدة سنوات ولم يكتشف مبكرا ما أدى إلى هشاشة وكسور في العظام. ارتفاع ضغط الدم وقصر قامته. تم علاجه بواسطة استئصال الغدة الكظرية بواسطة المنظار. أما المريضة الثانية فتبلغ من العمر 40 عاما وتم علاجها بواسطة إزالة الغدة النخامية من خلال فتحة الأنف. تم شفاء المريضين تماما. في هذا المقال وصف كامل لفوائد ومساوئ كلتا العمليتين والطريقة المثلى لعلاج هذا النوع من الأمراض.

مفتاح الكلمات: مرض كوشينغ، الجراحة، الغدة النخامية، التنظير الداخلي، استئصال الكظر، تقرير حالة، عمان.

ABSTRACT We describe two patients of the Department of Medicine at Sultan Qaboos University Hospital, Muscat, Oman, with Cushing's disease. Their magnetic resonance imaging scans of the pituitary were negative. One patient was treated by transsphenoidal surgery and the other by bilateral endoscopic adrenalectomy. Both procedures were successful and the patients cured. The advantages and disadvantages of these two approaches are discussed.

Key words: Cushing's disease; Surgery, pituitary; Endoscopy; Adrenalectomy; Case report; Oman.

CUSHING'S DISEASE IS AN UNCOMMON AND complex disorder.¹ Only six cases have been seen at Sultan Qaboos University Hospital, (Oman) since 1986 (personal observation by Nicholas J Woodhouse). Cushing's disease is caused by excessive adrenocorticotrophic hormone (ACTH) production by a pituitary tumour² and must be distinguished from Cushing's syndrome, due to ectopic ACTH overproduction by endocrine tumours of the lung, pancreas and other rarer sites.³ In this article, we describe two patients with Cushing's disease whose pituitary magnetic resonance imaging (MRI) scans were negative. Additional studies were then required to document the presence of a pituitary lesion and exclude an ectopic ACTH source. Our adult female patient was

cured by transphenoidal surgery (TSS) and the young boy with growth retardation by bilateral endoscopic adrenalectomy. The reasons for these different therapeutic approaches are discussed below.

CASE 1

A 40-year-old English woman was referred for further investigation of recent onset hypertension. On examination, central obesity was observed. She also had ulcerated mosquito bites on both shins that had not healed for four months. Cushing's syndrome was suspected clinically and ACTH dependant disease confirmed by finding raised cortisol and ACTH levels. Cortisol levels were suppressed by more than 50% by high dose dexamethasone which suggested pituitary

Table 1: Cortisol levels both patients after dexamethasone given 2 mg 6 hourly for 48 hours

	Cortisol nmol/l	Cortisol nmol/l
	Before dexametasone	After dexametasone
Patient 1	861	344
Patient 2	812	40

disease. As there was no evidence of a pituitary or ectopic tumour on the MRI or computed tomography (CT) scans, her disorder was initially controlled using oral ketaconazole and metyrapone. She was then referred to the endocrine unit at the Hammersmith Hospital in London where she underwent selective inferior petrosal sinus sampling with ACTH measurement following the intravenous administration of cortisol releasing hormone. This confirmed the presence of a left-sided pituitary lesion, and subsequently the left side of the pituitary gland was blindly removed by TSS surgery. Histology revealed a basophilic tumour positive for ACTH on immunofluorescence. She remains well four years later, only taking replacement thyroxine.

CASE 2

A 14-year-old boy was referred with a five-year history of growth retardation, hypertension, obesity, delayed sexual development (testosterone 1.8 (n = 6-27nmol/l)) and severe low back pain. Earlier studies had shown ACTH levels repeatedly within the 'normal' (4.2, 4.0, 3.5 [n=2.2-10.0pmol/l]) range at a time when his cortisol levels were elevated (923, 918, 812 [n = 240-620nmol/L]). Upon examination, he was clinically short with a height of 128 cm, and cushingoid features. His BP was 140/80 on lisinopril. An X-ray of the lumbar spine revealed severe loss of bone mineral density and multiple wedge compression fractures [Figure 1]. The bone densitometry was very low at 0.542 g/cm². Cortisol levels were suppressed by 95% after high dose dexamethasone suppression [Table 1] indicative of pituitary ACTH production, but as in Case 1, there was no evidence of a pituitary tumour on his initial MRI scan. Ectopic ACTH production was deemed unlikely in the absence of any obvious source on the CT or MRI scans of the lungs or abdomen; furthermore, the administration of octreotide (100 mcg 8 hourly subcutaneously for 3 days), failed to lower his cortisol levels. The patient then under-



Figure 1: Patient 2. X-Ray of the lumbar spine showing severe loss of bone mineral density with multiple wedge compression fractures in the lower dorsal and upper lumbar vertebral body (D12 & 4)

went bilateral laparoscopic adrenalectomy rather than pituitary surgery, as there were concerns that his subsequent growth and sexual development might be adversely affected. The histology revealed bilateral adrenal hyperplasia. Within twenty-six months of taking replacement hydrocortisone and fludrocortisone his



Figure 2: (Patient 2) Magnetic resonance imaging of the pituitary (T1W sagittal image, 2007) shows an 8 mm hypointense lesion in anterior lobe (microadenoma) after adrenalectomy.

height had increased from 123 to 140 cm and testosterone from 1.8 to 10.1 nmol/l. Unfortunately, there was only minimal improvement of his bone mineral density 0.554 g/cm², but his total skeletal calcium must have increased considerably having grown 17cm. We expect his bone mineral density to increase when his growth spurt is completed. Twenty six months later, however, he had become more pigmented, the ACTH level having increased from 4 to 22.6pmol/L and he developed an obvious microadenoma in the anterior lobe of the pituitary [Figure 2]. He was then referred for TSS abroad.

DISCUSSION

Both of these patients had Cushing's disease but their pituitary tumours were not visible on MRI at presentation. This is reportedly the case in up to 40 % of newly diagnosed patients.³ In these circumstances, therapeutic decision-making becomes more difficult as invasive measures are required to document the pituitary origin of the excess circulatory ACTH levels before referral for surgery. The first patient underwent cannulation with sampling of the petrosal sinus veins, and later removal of the left half of her pituitary gland. The disease was cured, but five years later she still requires thyroxine replacement therapy. Varying

degrees of postoperative hypopituitarism are seen in 30-40 % of all cases particularly those whose surgery is carried out blindly as in this case.⁴ Recently the European Cushing's disease survey group reviewed 668 patients: major non-hormonal complications of transseptosphenoïdal occurred in 14.5% of the patients; hypogonadism in 14-53%; hypothyroidism in 14-40%, and severe growth hormone deficiency in 13%.⁵ We concluded that the second patient also had pituitary dependant disease evidenced by his response to high dose dexamethasone⁶ and an absence of any obvious ectopic ACTH source on CT or MRI scanning of the lungs and abdomen. Furthermore, there was no response to octreotide; cortisol levels are usually unchanged in Cushing's disease whereas a fall is observed in patients with ectopic ACTH production as such tumours express somatostatin receptors.⁷ In the 14 year-old boy whose complaints were short stature and back ache, we were faced with two options: either to refer him abroad for petrosal sinus sampling and pituitary surgery, or to remove his adrenals. The former procedure would involve the risk of developing growth or sex hormone deficiencies⁵ whereas adrenalectomy by laparoscopy is safe and immediately curative.⁸ Moreover, the patient's sphenoid sinus had failed to pneumatise making a transsphenoidal approach more difficult. We therefore proceeded with laparoscopic bilateral adrenalectomy. Nelson's syndrome, characterized by accelerated growth of the pituitary tumour in the face of postoperatively reduced cortisol levels, occurs in between 8 and 38%^{9,10} of patients with Cushing's disease after adrenalectomy, usually 7 to 24 years after surgery.^{11, 12} After 26 months, he became more pigmented, his ACTH level increased and an MRI scan showed an 8 mm anterior lobe tumour [Figure 2]. The rapid growth of our patient's tumour is unusual and might have been related to the dramatic response to dexamethasone evidenced by a 95% reduction of his cortisol level during testing. This observation prompted us to speculate that patients with Cushing's disease who have the most dexamethasone sensitive pituitary tumours are more likely to develop Nelson's syndrome following adrenalectomy than those whose tumours are more resistant. However, in two other reports, the degree of susceptibility to the dexamethasone suppression test did not provide evidence for prediction of Nelson's syndrome.⁹⁻¹² Age itself appears to be important; Nelson's syndrome being more common in young patients

and rare after the age of 40.⁹ The patient has now been referred for TSS abroad.

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