ORIGINAL ARTICLES

Transsphenoidal surgery for pituitary tumours

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Abstract

Objectives—**Transsphenoidal surgery (TSS) is the preferred method for the excision of pituitary microadenomas in adults. This study was carried out to establish the long term efficacy and safety of TSS in children.**

Study design—**A 14 year retrospective analysis was carried out on 23 children (16 boys and seven girls), all less than 18 years of age, who had undergone TSS at our centre.**

Results—**Twenty nine transsphenoidal surgical procedures were carried out. The most common diagnosis was an adrenocorticotrophic hormone (ACTH) secreting adenoma (14 (61%) patients). The median length of follow up was 8.0 years (range 0.3–14.0 years). Eighteen (78%) patients were cured after the first procedure. No death was related to the operation. The most common postoperative complication was diabetes insipidus, which was transient in most patients. Other complications were headaches in two patients and cerebrospinal fluid leaks in two patients. De novo endocrine deficiencies after TSS in children were as follows: three (14%) patients developed panhypopituitarism, eight (73%) developed growth hormone insufficiency, three (14%) developed secondary hypothyroidism, and four (21%) developed gonadotrophin deficiency. Permanent ACTH deficiency occurred in five (24%) patients, though all patients received postoperative glucocorticoid treatment until dynamic pituitary tests were performed three months after TSS.**

Conclusions—**TSS in children is a safe and effective treatment for pituitary tumours, provided it is performed by surgeons with considerable experience and expertise. Surgical complications are minimal. Postoperative endocrine deficit is considerable, but is only permanent in a small proportion of patients.**

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Transsphenoidal surgery (TSS) was developed at the turn of the century.[1] The transcranial approach was originally favoured because it allowed clearer visualisation of the pituitary gland in the era before the operating microscope was developed. Between 1912 and 1925 Cushing modified the original mutilating transseptal transsphenoidal method of Gadiano by using a translabial approach.[2 3] When Hardy revived this method in the late 1960s,[4 5] it superseded the transcranial approach in popularity.

Since then there have been numerous publications on the outcome of TSS for various pituitary tumours generally,[6–9] and for Cushing's disease specifically.[10–16] Few reports have been published on the outcome of TSS in children and most have been limited to cases of Cushing's disease.[17–21] We have reviewed our experience with TSS in patients aged 18 years and less at the time of the operation. We report here the outcome in these patients, some of whom have been followed up long term (up to 14 years).

Patients and methods

We performed a retrospective analysis of all children less than 18 years old who had been under the care of two paediatric endocrinologists (CGDB and PCH) and had undergone TSS at our centre.

Twenty three patients (16 boys and seven girls) were identified dating back to 1982. Their age at operation ranged from 8.3 to 17.1 years. Twelve children had Cushing's disease, one had Cushing's disease as part of multiple endocrine neoplasia type 1, one had Nelson's syndrome, two had pituitary gigantism, two had non-functioning pituitary adenomas, two had craniopharyngiomas, one had a pituitary germinoma, one had a prolactinoma, and one had a Rathke's pouch cyst. Their clinical features are shown in table 1 (adrenocorticotrophic hormone (ACTH) secreting tumours) and table 2 (non-ACTH secreting tumours).

The two patients with pituitary gigantism (patients 15 and 16) presented with tall stature (height SD score +3.6 and +4.3, respectively) and increased growth velocity (height velocity SD score +1.2 and +7.1, respectively), despite being postpubertal and prepubertal, respectively. Patient 19 was referred to our centre for consideration of TSS after the recurrence of his craniopharyngioma, which had been treated previously with transcranial resection and cranial irradiation. Patient 21 (pituitary germinoma) had been followed up annually because of idiopathic diabetes insipidus diagnosed at

the age of 6 years. The two patients who had pubertal arrest/delay (patient 18, non-functioning pituitary adenoma and patient 22, prolactinoma) did not grow adequately after treatment with sex steroids to induce puberty.

PREOPERATIVE ENDOCRINE TESTS
In addition to tests specifically aimed at establishing the diagnosis in the different diagnostic groups, most patients underwent dynamic pituitary function tests in the form of a standard combined insulin tolerance test and a luteinising hormone releasing hormone and thyrotrophin releasing hormone test. Growth hormone insufficiency was defined as a peak serum growth hormone concentration of less

than 13.5 mU/l.[22] ACTH deficiency was defined as a peak serum cortisol concentration of less than 300 nmol/l or the absence of an incremental rise of 250 nmol/l.

In patients with suspected diabetes insipidus the diagnosis was confirmed on the basis of a documented mismatch of plasma and urine osmolality which corrected with the administration of 1-deamino-8-D-arginine vasopressin.

Patients 1–13 (Cushing's disease)
All patients with clinical features of Cushing's disease showed a loss of circadian rhythm of serum cortisol and ACTH concentrations, defined as a sleeping midnight serum cortisol of greater than 50 nmol/l[23] and a simultaneously

Table 1 Clinical features of 14 children with ACTH secreting pituitary tumours (13 with Cushing's disease and 1 with Nelson's syndrome)

Patient No	Sex	Diagnosis	Length of history (years)	Age at operation (years)	Height (cm)	Height SD score	Bone age (years)	Weight gain	Cushingoid appearance*	Acne	Hirsutism	Blood pressure	Pubertal development (ratings)
1	F	Cushing's disease	1.0	15.5	156.0	−1.1	Not recorded	+	+	+	+	120/80	Concordant (B2, P2, A2, M0)
2	F	Cushing's disease	3.0	13.1	140.2	−2.2	11.0	+	+	−	−	120/95(↑)	Concordant (B3, P2, A2, M0)
3	F	Cushing's disease	4.5	16.3	154.1	−1.5	15.0	+	+	−	−	120/80	Concordant (B5, P5, A3, M1)
4	F	Cushing's disease	4.0	13.2	138.6	−2.5	12.5	+	+	+	+	120/70	Concordant (B3, P4, A3, M0)
5	F	Cushing's disease	3.0	11.8	135.7	−1.8	11.0	+	+	+	+	110/80	Discordant (B2, P3, A3, M0)
6	M	Cushing's disease	1.0	14.8	160.0	−1.0	Not recorded	+	+	+	+	120/90(↑)	Concordant (G5, P5, A3, 20,20)
7	M	Cushing's disease	3.0	14.9	146.8	−2.6	13.0	+	+	+	+	110/60	Discordant (G5, P5, A3, 08,08)
8	M	Cushing's disease	4.0	16.2	147.0	−3.6	14.4	+	+	−	−	130/80	Delayed (G1, P1, A1, 02,02)
9	M	Cushing's disease	1.5	12.8	143.2	−1.3	Not recorded	+	+	+	+	140/80	Discordant (G3, P4, A3, 03,03)
10	M	Cushing's disease	1.5	14.1	145.0	−2.2	13.0	+	+	+	+	120/75	Concordant (G2, P2, A2, 03,03)
11	M	Cushing's disease	2.0	16.2	159.7	−1.9	15.6	+	+	+	+	120/80 (on treatment)	Concordant (G3, P4, A3, 08,08)
12	M	Cushing's disease	4.0	14.3	147.7	−2.0	15.9	+	+	+	+	145/120 (↑)	Discordant (G2, P5, A2, 04,04)
13†	M	Cushing's disease/MEN type 1	0.5	8.7	129.6	−0.4	7.8	+	+	−	−	135/90 (↑)	Prepubertal (G1, P2, A1, 02,02)
14‡	M	Nelson's syndrome	0.8	16.9	164.1	−1.6	Not recorded	−	−	−	−	110/70	Concordant (G5, P5, A3, 15,15)

* Moon face, buffalo hump, truncal obesity, and striae.
† Patient with an extensive family history of multiple endocrine neoplasia (MEN) type 1.
‡ Patient presented originally with Cushing's disease aged 12 years and underwent bilateral adrenalectomies elsewhere. Represented with skin hyperpigmentation and headaches.

Table 2 Clinical features of nine children with non-ACTH secreting tumours

Patient No	Sex	Diagnosis	Length of history (years)	Age at operation (years)	Height (cm)	Height SD score	Bone age (years)	Symptoms and signs
15	M	Pituitary gigantism	2.0	16.8	201.0	3.6	16.6	Tall stature and increased growth velocity. Pubertal ratings G5, P5, A3, 20, 20
16	M	Pituitary gigantism	4.0	9.9	164.0	4.3	11.0	Tall stature and increased growth velocity. Pubertal ratings G1, P1, A1, 02, 02
17	M	Non-functioning pituitary tumour	5.0	13.6	141.0	−2.2	12.0	Short stature and growth arrest. Pubertal ratings G2,P 2, A1, 06, 06
18	M	Non-functioning pituitary tumour	3.0	17.1	178.4	0.4	15.0	Growth and pubertal arrest. Pubertal ratings G3, P1, A1, 08, 10
19	M	Craniopharyngioma	< 0.1	8.3	124.0	−1.9	Not recorded	Recurrence of a craniopharyngioma resected elsewhere transcranially at the age of 3 years. Presented with headaches and vomiting
20	M	Craniopharyngioma	5.0	10.3	120.7	−3.0	5.4	Short stature and poor growth for five years. Pale optic discs
21	M	Pituitary germinoma	1.0	13.7	143.6	−2.0	12.9	Growth arrest documented at follow up for cranial diabetes insipidus diagnosed aged 6 years
22	F	Prolactinoma	5.0	16.1	150.0	−2.2	12.2	Short stature, poor growth, and delayed puberty (no breast development at 15.9 years). Galactorrhoea
23	F	Rathke's pouch cyst	5.0	10.1	124.8	−2.2	6.7	Poor growth since the age of 5 years

Table 3   Duration of follow up and outcome after TSS

Patient No	Diagnosis	Surgeon	Follow up (years)	Outcome
1	Cushing's disease	MP	9.5	Cured
2	Cushing's disease	MP	8.0	Cured
3	Cushing's disease	MP	5.5	Cured
4	Cushing's disease	MP	4.0	Cured
5	Cushing's disease	MP	1.0	Cured
6	Cushing's disease	RAW	14.0	Cured
7	Cushing's disease	RAW	12.5	Cured
8	Cushing's disease	MP	8.0	Cured
9	Cushing's disease	MP	3.0	Cured
10	Cushing's disease	MP	3.0	Recurrence. Cured after second TSS
11	Cushing's disease	MP	7.0	Recurrence after second TSS and pituitary irradiation. Had bilateral adrenalectomies
12	Cushing's disease	MP	6.5	Recurrence after second TSS. Cured after third TSS and pituitary irradiation
13	Cushing's disease/MEN type 1*	MP	9.0	Persistent Cushing's disease. Cured after second TSS
14	Nelson's syndrome	RAW	12.0	Cured
15	Pituitary gigantism	RAW	12.0	Cured
16	Pituitary gigantism	MP	6.5	Cured
17	Non-functioning pituitary tumour	RAW	12.0	Cured
18	Non-functioning pituitary tumour	RAW	11.0	Cured
19	Craniopharyngioma	MP	5.0	Recurrent disease. Further TSS, craniotomies, and radiotherapy. Died of underlying disease
20	Craniopharyngioma	MP	0.3	Cured
21	Pituitary germinoma	RAW	12.0	Cured
22	Prolactinoma	MP	9.3	Cured
23	Rathke's pouch cyst	MP	0.3	Cured

* MEN = multiple endocrine neoplasia.

detectable serum ACTH. All but one patient (patient 5) had an increased urinary free cortisol concentration (>250 nmol/l). A low dose dexamethasone test (0.5 mg of dexamethasone by mouth every six hours for 48 hours) was performed in 10 of the 13 patients. Only two patients suppressed to less than 50 nmol/l (patients 5 and 10).[23] All 13 patients suppressed to less than 50% of baseline serum cortisol concentration when they underwent the high dose dexamethasone suppression test (2.0 mg of dexamethasone by mouth every six hours for 48 hours).[24] Patients 1, 3, 6, 12, and 13 also had growth hormone insufficiency.

Patients 14–23
The patient with Nelson's syndrome had grossly increased serum ACTH levels, ranging from 1727 to 3202 ng/l (upper limit of normal 82 ng/l). Apart from cortisol and aldosterone deficiency secondary to bilateral adrenalectomies, he had otherwise normal pituitary function.

The two patients with pituitary gigantism had increased serum growth hormone concentrations throughout a 24 hour period, with sampling intervals of 20 minutes. Neither patient suppressed their serum growth hormone concentrations after a glucose load of 75 g (oral glucose tolerance test). Both patients had otherwise normal endocrinology.

The patient with prolactinoma had grossly increased serum prolactin concentrations, greater than 5400 mU/l on repeated occasions (upper limit of normal 660 mU/l). In addition, she had growth hormone insufficiency, but otherwise normal endocrinology.

Patients 17 and 23 had isolated growth hormone insufficiency. Patients 18 and 19 had panhypopituitarism. Patients 20 and 21 had growth hormone insufficiency and gonado-

trophin deficiency. In addition, patient 21 had thyroid stimulating hormone deficiency.

IMAGING
All patients underwent cranial imaging with pituitary views using high resolution computed tomography in the earlier years, or magnetic resonance imaging, or both. Where indicated, patients with Cushing's disease underwent further imaging in the form of computed tomography of the adrenal glands and chest to exclude a non-pituitary cause for Cushing's syndrome. Simultaneous bilateral inferior petrosal sinus sampling for plasma ACTH[25–27] was performed in four patients with Cushing's disease where the source of excess ACTH was still in question.

TRANSSPHENOIDAL SURGERY
Translabial TSS was performed by a consultant neurosurgeon (MP) in 16 patients and in seven by a consultant otolaryngologist (RAW) in the earlier years (table 3). Microadenomectomy was performed unless a tumour could not be identified intraoperatively, in which instance the anterior lobe of the pituitary gland was resected. In the two patients with craniopharyngioma, the cystic component of the tumour was marsupialised into the sphenoid air sinuses.

POSTOPERATIVE ASSESSMENT
Cure was defined as a resolution of the clinical symptoms and signs and, where appropriate, normalisation of the underlying preoperative endocrine abnormality. All patients underwent a combined insulin tolerance test and a luteinising hormone releasing hormone and thyrotrophin releasing hormone test within three months of the operation.

Results

Twenty three patients underwent 29 transsphenoidal pituitary operations. The median length of follow up was 8.0 years (range 0.3–14.0 years).

PATIENTS CURED AFTER FIRST TSS

Most patients (18 patients; 78%) were cured after the first operation, though the postoperative follow up period for a few of these is short (table 3). Two patients required radiotherapy for their underlying disease (patients 20 and 21). The patient with prolactinoma had a persistent mild increase in her serum prolactin, ranging from 600 to 1000 mU/l (upper limit of normal 660 mU/l), which has been well controlled with dopamine agonists. Repeated magnetic resonance imaging of the pituitary gland have not shown a recurrence of her prolactinoma nine years after the operation. The patient with Nelson's syndrome had a normal serum ACTH concentration at follow up. Postoperative investigations of the two patients with pituitary gigantism showed normal 24 hour serum growth hormone profiles and normal suppression of serum growth hormone secretion after a 75 g glucose load by mouth. All patients cured of their Cushing's disease showed restoration of the normal circadian pattern of serum cortisol concentration and a normal 24 hour urinary free cortisol concentration.

PATIENTS NOT CURED AFTER FIRST TSS

Five patients (four with Cushing's disease and one with craniopharyngioma) underwent further TSS (table 3).

Patient 10 had a clinical and biochemical relapse one year after TSS. Imaging of his chest and adrenal glands was normal. Magnetic resonance imaging of his pituitary gland confirmed the presence of a tumour, which was then removed by TSS. He remains in remission 16 months later.

Patient 11, in whom a pituitary tumour had been seen on computed tomography and confirmed histologically at operation, developed clinical and biochemical relapse of Cushing's syndrome 10 months after TSS. Computed tomography of his adrenal glands was normal and simultaneous bilateral inferior petrosal sinus sampling localised the tumour to the left side of the pituitary, from where it was removed by a second TSS. The patient underwent pituitary irradiation, but relapsed nine months later. Bilateral adrenalectomies were then performed. Histological examination of the adrenal glands showed diffuse bilateral adrenal hyperplasia. He remains well five years later while receiving hydrocortisone and fludrocortisone replacement.

Patient 12, in whom a pituitary tumour was seen on computed tomography and who had normal adrenal and chest imaging, remained cushingoid three months after TSS. Endocrine tests confirmed persistent hypercortisolaemia. No tumour was seen on computed tomography of the pituitary gland, adrenal glands, or chest. At re-exploration of the pituitary gland transsphenoidally a tumour was found and resected.

Despite a good initial clinical response, the patient relapsed nine months later. Magnetic resonance imaging of the pituitary gland showed a tumour. Simultaneous bilateral inferior petrosal sinus sampling also localised the tumour to the pituitary gland, but did not lateralise it. A tumour was resected at a third TSS. The patient received pituitary irradiation and has shown no sign of relapse four years later.

Patient 13, in whom a pituitary tumour was seen and resected at TSS and was confirmed histologically and on immunohistochemical staining, remained cushingoid six months after TSS. Computed tomography of the pituitary gland, adrenal glands, and chest before the first and second TSS did not show a tumour. No tumour was seen at the second procedure. The anterior lobe of the pituitary gland was resected. Histological examination confirmed an adenoma. He remains cured of his Cushing's disease nine years later.

The patient with craniopharyngioma (patient 19) underwent further TSS two years after the first procedure to resect a recurrence. He had a particularly aggressive tumour which did not respond to yttrium implants and focal stereotactic radiotherapy. Several transcranial cyst drainage procedures were undertaken. He died five years after the first TSS from wide intracranial spread of his craniopharyngioma.

PITUITARY IMAGING, SURGICAL AND HISTOLOGICAL FINDINGS

A tumour was identified on pituitary imaging (computed tomography or magnetic resonance imaging) in all nine patients with non-ACTH secreting tumours and in the patient with Nelson's syndrome, but in only four of the patients with Cushing's disease. Eighteen computed tomographic scans identified three macroadenomas and nine microadenomas. Ten magnetic resonance scans identified one macroadenoma and three microadenomas. Bilateral simultaneous inferior petrosal sinus sampling was performed in four patients with Cushing's disease. It confirmed a pituitary source of the excess ACTH production in all four and was able correctly to lateralise the lesion within the gland in two patients.

In all but one patient (patient 8) a tumour was seen at the first TSS. All surgical specimens were examined histologically. The specimens from six patients with Cushing's disease and those from patients 19–23 showed diagnostic histological features. Immunohistochemical staining was performed on seven surgical specimens from patients with Cushing's disease. Three specimens expressed ACTH exclusively; one of these specimens had shown normal histological features on ordinary staining.

POSTOPERATIVE COMPLICATIONS

There were no deaths related to the operation. One patient with craniopharyngioma (patient 19) died of his underlying disease five years after undergoing TSS. The most common postoperative complication was diabetes insipidus, which developed in 15 patients (72%); two patients were already receiving 1-deamino-8-D-arginine vasopressin replacement treat-

Table 4 Endocrine deficit before and after transsphenoidal surgery and duration of postoperative glucocorticoid replacement treatment

Patient No	Diagnosis	Preoperative endocrine deficit	Postoperative endocrine deficit*	Duration of glucocorticoid replacement (years)
1	Cushing's disease	GH	GH, gonadotrophins, ACTH, ADH	Permanent
2	Cushing's disease		GH, ACTH	3.0
3	Cushing's disease	GH	ACTH	2.0
4†	Cushing's disease		ACTH	4.0
5†	Cushing's disease		GH, ACTH	1.0 (being reduced)
6	Cushing's disease	GH	GH, ACTH	3.0
7	Cushing's disease		GH, ACTH	2.0
8	Cushing's disease		GH, TSH, gonadotrophins, ACTH	Permanent
9†	Cushing's disease		GH, ACTH	1.0
10†	Cushing's disease		GH	< 0.3
11†	Cushing's disease		GH, ACTH	0.5
12	Cushing's disease	GH	GH, TSH, gonadotrophins, ACTH	Permanent
13	Cushing's disease/MEN type 1	GH	GH, TSH, gonadotrophins, ACTH	Permanent
14	Nelson's syndrome	Cortisol and aldosterone	GH, cortisol, aldosterone	Permanent
15	Pituitary gigantism		ADH	< 0.3
16	Pituitary gigantism			< 0.3
17	Non-functioning pituitary tumour	GH	GH, ADH	< 0.3
18	Non-functioning pituitary tumour	GH, TSH, gonadotrophins, ACTH	GH, gonadotrophins, ACTH	3.0
19	Craniopharyngioma	GH, TSH, gonadotrophins, ACTH, ADH	GH, TSH, gonadotrophins, ACTH, ADH	Permanent‡
20	Craniopharyngioma	GH, TSH, gonadotrophins	GH, TSH, gonadotrophins	< 0.3
21	Pituitary germinoma	GH, gonadotrophins, ADH	GH, gonadotrophins, ACTH, ADH	Permanent
22	Prolactinoma	GH	GH	< 0.3
23	Rathke's pouch cyst	GH	GH	< 0.3

* Assessed three months after TSS.
† Insulin tolerance/luteinising hormone releasing hormone/thyrotrophin releasing hormone test not performed before TSS.
‡ Continued to receive treatment until death.
GH = growth hormone; ADH = antidiuretic hormone; and TSH = thyroid stimulating hormone.
MEN = multiple endocrine neoplasia.

ment and continued to need it long term (patients 19 and 21). Diabetes insipidus was transient in 12 of the 15 patients, requiring no 1-deamino-8-D-arginine vasopressin replacement, or treatment for a few days only. Two patients continued to need 1-deamino-8-D-arginine vasopressin replacement for six months after TSS (patients 15 and 17) and one permanently (patient 1).

Other complications included headaches, which lasted for three months in two patients. Cerebrospinal fluid leaks developed in two patients; one settled spontaneously within two days while the other persisted for two months, necessitating the insertion of a lumbar drain.

POSTOPERATIVE ENDOCRINE DEFICIT
Table 4 shows details of endocrine deficit in all 23 patients before and after TSS. Two patients (patients 18 and 19) had panhypopituitarism before TSS. Of the remainder, three (14%) patients (patients 8, 12, and 13) developed panhypopituitarism de novo after resection of the anterior lobe of the pituitary gland, either at first or repeat TSS.

Twelve patients had growth hormone insufficiency before TSS. Eight of the remaining patients (73%) became insufficient in growth hormone after TSS, five of whom needed treatment with recombinant human growth hormone until their final height was attained. One patient is currently being considered for recombinant human growth hormone treatment in adult life. One patient (patient 3) regained normal growth hormone status after TSS. Three (14%) patients developed second-

ary hypothyroidism after TSS and continue to receive thyroxine replacement treatment. Gonadotrophin deficiency developed in four (21%) patients after TSS. Sex steroid replacement treatment was instituted at the appropriate age in all four.

All patients received postoperative glucocorticoid replacement treatment (hydrocortisone or prednisolone) until dynamic pituitary tests were performed two months after TSS. ACTH deficiency was documented in 13 (62%) patients after TSS. Permanent ACTH deficiency consequent to TSS, as indicated by the need for continued glucocorticoid replacement treatment, occurred in only five (24%) patients. The median time for recovery of the hypothalamo-pituitary-adrenal axis and discontinuation of glucocorticoid replacement treatment was 2.0 years (range 0.5–4.0).

Discussion
TSS is the surgical treatment of choice for many types of pituitary tumours and is the first line treatment for Cushing's disease in adults.[28][29] We have reported here our experience with TSS performed in children, namely that it is a safe and effective treatment for various types of pituitary microadenomas and macroadenomas in this age group.

This study, in which most patients have been followed up long term, provides important data on the outcome of TSS in children. Successful surgical treatment for all tumours after the first procedure was seen in 78% of patients. For ACTH secreting tumours the success rate was slightly lower at 71%, which is comparable with

large adult series[13–15] and paediatric series of similar size,[17 18 20 30] though one series reported a lower cure rate of 50% for Cushing's disease in childhood.[21] For non-ACTH secreting tumours the operative cure rate was approximately 90%, higher than that reported in other paediatric series.[31] Surgical morbidity was minimal. Most patients were discharged within seven days of TSS. Postoperative headaches and cerebrospinal fluid leaks occurred in only two of 29 surgical procedures. There were no deaths from the surgical procedure itself. One patient died from wide intracranial spread of his craniopharyngioma. He relapsed despite apparently adequate previous transcranial resection of his tumour on two occasions, pituitary radiotherapy, adequate transsphenoidal clearance of the recurrent tumour, and a number of drainage procedures for the cystic component of the tumour. Yttrium implants did not control his disease, nor did stereotactic radiotherapy.

Unsuccessful surgical treatment or recurrence after the first procedure was not a contraindication to a second or even third attempt. Two of the four patients with Cushing's disease were cured after a second TSS. The two remaining patients required further surgical and therapeutic interventions. The size of the tumour was no bar to TSS, though large tumours are less amenable to the transsphenoidal approach.[32] Success of this operation is related to the expertise of the surgeon performing it. We recommend that pituitary surgery of this highly specialised nature should be performed only by those who do considerable numbers of pituitary microadenoma operations. This is particularly important in children as pituitary tumours are rare. At our centre all transsphenoidal operations are now performed by one neurosurgeon, though in earlier years an ear, nose, and throat surgeon undertook such procedures.

Hypopituitarism is an important long term consequence of TSS. Resection of the tumour itself, as opposed to the whole gland, may reduce the risk of multiple pituitary hormone deficiency. In our series the three patients who developed panhypopituitarism after TSS were those who had undergone complete resection of the anterior lobe of the pituitary gland because the tumour could not be seen at the time of the operation, either at first or repeat attempts. The most common endocrine deficiencies which developed after TSS were growth hormone insufficiency (73%) and antidiuretic hormone deficiency (72%). The latter was transient in most, only one patient (5%) developing permanent diabetes insipidus. Although growth hormone insufficiency was a common postoperative complication, only 33% of those who developed the disorder needed treatment with recombinant human growth hormone to realise their growth potential. Secondary hypothyroidism and gonadotrophin deficiency were rarer complications, but required permanent replacement treatment.

All our patients were treated with glucocorticoid supplements to avoid the precipitation of a postoperative addisonian crisis, particularly in patients with Cushing's disease, in whom a serum cortisol concentration of <50 nmol/l on the fifth postoperative day is regarded as cure.[33] Assessment of pituitary function at three months showed a persistent poor cortisol response to insulin induced hypoglycaemia, presumably secondary to ACTH insufficiency, in 62% of the patients; this was permanent in 24%. The time taken for the hypothalamo-pituitary-adrenal axis to recover was as long as four years, with a median of two years. This has important practical implications in the follow up of patients who have undergone TSS.

Although cranial imaging (computed tomography and magnetic resonance imaging) was undertaken in all our patients, it was only reliably diagnostic in non-ACTH secreting tumours (100% in our series). The overall accuracy of computed tomography for detecting ACTH secreting tumours was only 40% in our series, compared with a reported 62% by Marcovitz *et al.*[34] The low pick up rate is attributed to the size of these tumours, which are usually small microadenomas (less than 6 mm in diameter). Although magnetic resonance imaging is reported to be superior to computed tomography in detecting pituitary microadenomas,[35 36] this was not so in our series. In the three patients in whom both computed tomography and magnetic resonance imaging were performed, magnetic resonance imaging did not add to the diagnostic process. In our experience it is of limited use in diagnosing ACTH secreting tumours.

Pituitary imaging, however, gives the surgeon valuable preoperative information about the local anatomy, the degree of pneumatisation of the sphenoid air sinuses, the size and site of the tumour (if seen), and hence the feasibility of the transsphenoidal approach. Pneumatisation of the sphenoid air sinuses may not be equal on the two sides, thereby resulting in an asymmetrical sella turcica floor thickness. At the junction of the sphenoid septum with the sella floor there may be a slight depression of the floor simulating an area of pathological erosion. Alternatively, abnormalities in the floor of the fossa may provide a clue to the localisation of a microadenoma. Non-pneumatised sphenoid air sinuses may make the transsphenoidal approach less favourable, though this may depend on the preference of the individual surgeon. Bilateral simultaneous inferior petrosal sinus sampling is a valuable tool in localising the pathology to a pituitary origin in difficult cases of Cushing's syndrome. In some patients it may also lateralise the tumour to one side of the pituitary.[37] It is, however, an expensive and invasive procedure in which the success and complications depend on the operator's skill and experience. Complications range from inguinal haematoma to permanent damage to the brain stem.[38] We have found this investigation helpful in confirming a pituitary source of ACTH in four patients, but accurate localisation of the tumour was possible in only two. Our experience in these patients, albeit limited, suggests that the vascularity of the sinuses in children prevents accurate localisation.

Key messages

● Transsphenoidal surgery is a safe and effective treatment for pituitary tumours in children

● Transsphenoidal surgery should be performed by surgeons with considerable experience and expertise

● Surgical complications of transsphenoidal surgery are minimal and endocrine deficit is permanent in only a small proportion of patients

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Alternative surgical approaches to the treatment of pituitary tumours, such as transcranial surgery, carry a higher risk of operative mortality and morbidity.[39] In certain circumstances, however, TSS may not be suitable. Indications for the transcranial method include large suprasellar extension and spread of the tumour posteriorly in a retroclival direction or laterally over the cavernous sinus. Bilateral adrenalectomy for the treatment of Cushing's disease carries a significant risk of Nelson's syndrome[40] as well as the need for life long glucocorticoid and mineralocorticoid replacement treatment. Pituitary irradiation for Cushing's disease and other radiosensitive tumours is associated with a high relapse rate and takes many years for full therapeutic results to emerge,[41] so is best reserved as adjunctive treatment.[42]

We conclude that TSS for pituitary tumours in children is curative in most patients. The operative procedure is safe and is associated with a low morbidity. Although hormonal deficiencies are common, only a small proportion of patients require permanent replacement treatment.

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